PATENT
ATTORNEY DOCKET NO.: 054945-0023

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 5,250,542)
Granted: October 5, 1993)
)
Patentees: Buddy E. CANTRELL *et al.*)
)
Assignee: Eli Lilly and Company)
)
FOR: PERIPHERALLY SELECTIVE)
PIPERIDINE CARBOXYLATE OPIOID)
ANTAGONISTS)

Commissioner for Patents
U.S. Patent and Trademark Office
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Randolph Building
401 Dulany Street
Alexandria, VA 22314

Date **June 17, 2008**

FEE COVER SHEET FOR
APPLICATION FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. § 156

Sir:

1. Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM PURSUANT TO 35 U.S.C. § 156 including Exhibits 1-15 (Original + 2 sets).

2. Constructive Petition

☒ EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

3. Fee Calculation (37 C.F.R. §1.16)

Fee for Patent Term Extension	$ 1,120.00
Reduction by ½ for filing by a small entity	$ 0.00
TOTAL FEE =	$ 1,120.00

4. Fee Payment

☒ The Commissioner is hereby authorized to charge **$1,120.00** to Deposit Account No. 50-0310 for Extension of Term of Patent (37 C.F.R. §1.20(j)(1) (PTO Fee Code 111).

☒ The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: June 17, 2008

By: _____

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Date **June 17, 2008**

APPLICATION FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. § 156

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156(a), Eli Lilly and Company (hereinafter "Applicant" or "Eli Lilly") hereby requests an extension of the patent term of United States Patent No. 5,250,542 (hereinafter variously referred to as "U.S. Patent No. 5,250,542" or "the '542 Patent").

Attention is called to the simultaneous filing by Applicant of a request for extension of the patent term of Applicant's United States Patent No. 5,434,171 based upon the same regulatory review period as the subject application, as authorized by 37 CFR § 1.785(b). It is understood that when these two patents are found to be eligible for patent term extension based on the same regulatory review period, that the final determination under 37 CFR § 1.750 will provide a period of

time for Applicant to elect the patent for which extension is desired, accompanied by an express withdrawal of the application for extension of the nonelected patent as provided in MPEP § 2761.

Applicant, Eli Lilly and Company, a corporation created and existing under the Laws of the State of Indiana, represents that it is the record owner of United States Patent No. 5,250,542, by reason of an assignment from the inventors thereof recorded on July 1, 1993 at Reel 006585, Frame 0364. A copy of the U.S. Patent and Trademark Office Abstract of Title confirming recordation of the Assignment is included in **Exhibit 1** hereto. The active moiety in the approved product that forms the basis for this application was initially developed at Eli Lilly (then designated as LY246736), and is exclusively licensed by Eli Lilly to Shire Pharmaceutical Group (formerly Roberts Pharmaceutical) under an agreement dated November 5, 1996 (including a license under U.S. Patent 5,250,542), and is exclusively sublicensed by Shire Pharmaceutical Group to Adolor Corporation under an option and license agreement dated June 10, 1998 (including a sublicense under U.S. Patent 5,250,542). The undersigned registered practitioner, Donald J. Bird (Reg. No. 25,323), is counsel for the marketing applicant (Adolor Corporation), and has been authorized to act on behalf of the patent owner (Eli Lilly) with respect to this Application and all correspondence pertaining thereto as set forth in section (15) below.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 *et seq.*, and follows the numerical sequence and format as set forth in 37 C.F.R. § 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is ENTEREG® (alvimopan) capsules. The active moiety of the approved product has the chemical name:

[[2(S)-[[4(R)-(3-hydroxyphenyl)-3(R),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid,

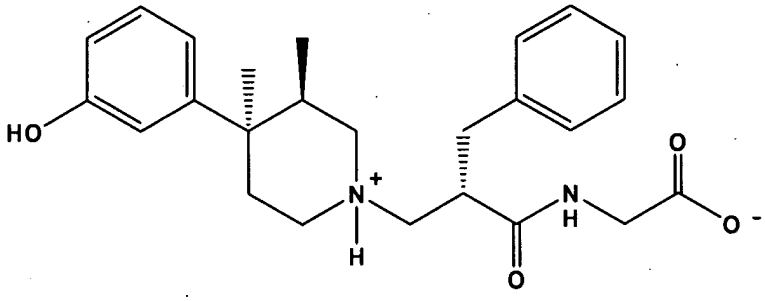
the molecular formula:

$C_{25}H_{32}N_2O_4$

a molecular weight of:

424.5;

and the structural formula:



and is present in the approved product in the dihydrate form, which has been assigned the USAN name of alvimopan. Alvimopan thus has the chemical name, as stated in Section 11 "Description" of the Approved Label (copy attached as **Exhibit 2**):

[[2(S)-[[4(R)-(3-hydroxyphenyl)-3(R),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate

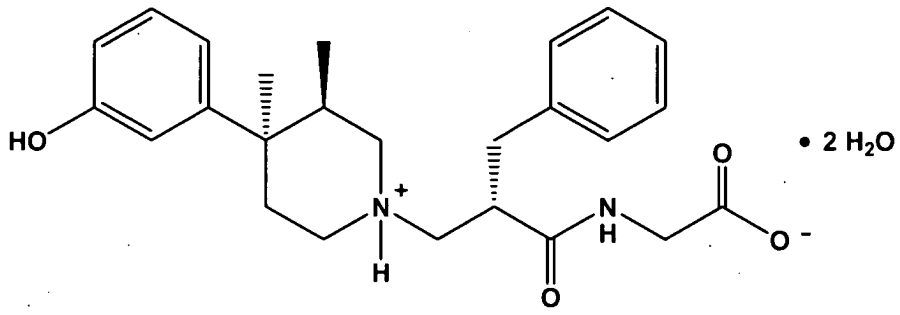
the molecular formula:

$C_{25}H_{32}N_2O_4 \bullet 2\ H_2O$

a molecular weight of:

460.6;

and the structural formula:



(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

ENTEREG® (alvimopan) Capsules was subject to regulatory review under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355(b)).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

ENTEREG® (alvimopan) Capsules received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355(b)) upon approval of NDA 21,775 on May 20, 2008.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient of the product ENTEREG® Capsules is alvimopan, which has not been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act prior to approval of NDA 21,775 on May 20, 2008.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved on May 20, 2008, and the last day within the sixty day period permitted for submission of an application for patent term extension is July 19, 2008.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

The complete identification of the patent for which an extension is being sought is as follows:

Inventors:	Buddy E. Cantrell Dennis M. Zimmerman
U.S. Patent No.:	5,250,542
Earliest Filing Date:	March 29, 1991
Grant Date:	October 5, 1993
Expiration Date:	March 29, 2011

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A full copy of U.S. Patent No. 5,250,542, for which extension is being sought, is attached as **Exhibit 3**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

A copy of Certificates of Correction, dated December 28, 1999 and June 26, 2007, are attached as **Exhibit 4**.

A copy of the maintenance fee statement showing timely payment of all maintenance fees when due is attached as **Exhibit 5**.

No disclaimer or reexamination certificate has been filed and/or issued for U.S. Patent No. 5,250,542.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product.

(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;

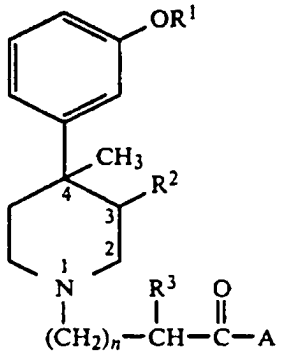
Claims of U.S. Patent No. 5,250,542 read on the approved product as detailed below.

Patent Claims to the Approved Product:

Claims 1, 2, 4, 5 and 10-15 of U.S. Patent No. 5,250,542 encompass (read on) the approved product.

Claim 1 reads as follows:

1. [As corrected by Certificate of Correction] A trans-3,4 isomer of a compound of the formula (I)



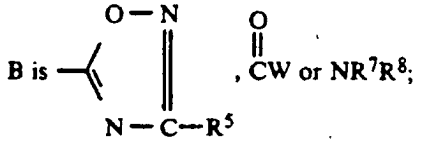
wherein

R^1 is hydrogen or C_1–C_5 alkyl;

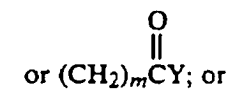
R^2 is hydrogen, C_1–C_5 alkyl or C_2–C_6 alkenyl;
R^3 is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3, alkyl C_5–C_8 cycloalkyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;

A is OR^4 or NR^5R^6 ;

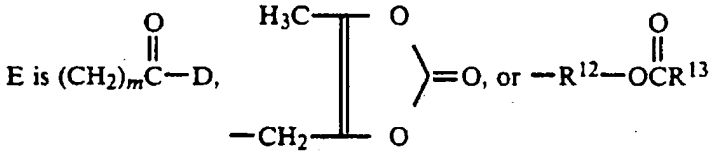
wherein:
R^4 is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;
R^5 is hydrogen or C_1–C_3 alkyl;
R^6 is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, cycloalkyl, phenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8cycloalkenyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, phenyl-substituted C_1–C_3 alkyl, or $(CH_2)_q$ —B; or
R^5 and R^6 together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;



R^7 is hydrogen or C_1–C_3 alkyl;
R^8 is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, cycloalkyl-substituted C_1–C_3 alkyl, cycloalkyl, C_5–C_8 cycloalkenyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, phenyl or phenyl-substituted C_1–C_3 alkyl; or
R^7 and R^8 together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;
W is OR^9, $NR^{10}R^{11}$, or OE;
R^9 is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;
R^{10} is hydrogen or C_1–C_3 alkyl;
R^{11} is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, phenyl-substituted C_1–C_3 alkyl,



R^{10} and R^{11} together with N form a saturated non aromatic 4- 6-membered heterocyclic ring;



R^{12} is C_1–C_3 alkyl substituted methylene, R^{13} is C_1–C_{10} alkyl;
D is OR^{14} or $NR^{15}R^{16}$;
wherein:
R^{14} is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, or C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;
R^{15} is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, phenyl-substituted C_1–C_3 alkyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl or C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl; and
R^{16} is hydrogen or C_1–C_3 alkyl; or
R^{15} and R^{16} together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;
Y is OR^{17} or $NR^{18}R^{19}$;
R^{17} is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, or phenyl-substituted C_1–C_3 alkyl;
R^{18} is hydrogen or C_1–C_3 alkyl; and
R^{19} is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, or phenyl-substituted C_1–C_3 alkyl; or
R^{18} and R^{19} together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;
n is 0-4;
q is 1-4;
m is 1-4;
or a pharmaceutically acceptable salt thereof.

The active ingredient of the approved product is chemically identified in Section 11 "Description" of the Approved Label at lines 2-4 as [[2(S)-[[4(*R*)-(3-hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate. **Claim 1 of U.S. Patent 5,250,542 reads on (encompasses) the approved product, when:**

R^1 is hydrogen;

R^2 is a C_1-C_5 alkyl (*i.e.*, CH_3);

n is 1;

R^3 is phenyl-substituted C_1-C_3 alkyl (*i.e.*, Ph-CH_2);

A is NR^5R^6;

R^5 is hydrogen;

R^6 is $(CH_2)_q$–B;

q is 1;

B is  ;

W is OR^9; and

R^9 is hydrogen.

* * * * *

Claim 2 reads as follows:

2. The compound of claim 1 wherein R^1 is hydrogen; R^2 is C_1–C_3 alkyl; n=1 or 2; and R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl.

Claim 2 is dependent on claim 1 and reads on (encompasses) the approved product for the reasons stated above, and more specifically when:

R^1 is hydrogen;

R^2 is a C_1-C_5 alkyl (*i.e.*, CH_3);

n is 1; and

R^3 is benzyl.

* * * * *

Claim 3 reads as follows:

4. The compound of claim 2 wherein A is NR^5 R^6 in which R^5 is hydrogen and R^6 is $(CH_2)_q$ —B wherein q is 1 to 3 and B is —C(O)W.

Claim 4 is dependent on claim 2 and reads on (encompasses) the approved product for the reasons stated above, and more specifically when:

A is NR^5R^6;

R^5 is hydrogen;

R^6 is $(CH_2)_q$–B;

q is 1; and

B is 

* * * * *

Claim 5 reads as follows:

5. The compound of claim 4 wherein W is OR^9 and R^9 is hydrogen, C_1–C_5 alkyl, phenyl-substituted C_1–C_2 alkyl, C_5–C_6 cycloalkyl, or C_5–C_6 cycloalkyl-substituted C_1–C_3 alkyl.

Claim 5 is dependent on claim 4 and reads on (encompasses) the approved product for the reasons stated above, and more specifically when:

W is OR^9; and

R^9 is hydrogen.

* * * * *

Claim 10 reads as follows:

10. The compound of claim 1 wherein the configuration at positions 3 and 4 of the piperidine ring is each R.

Claim 10 is dependent on claim 1 and reads on (encompasses) the approved product for the reasons stated above, and more specifically when:

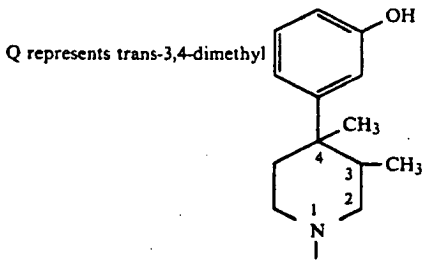
The configuration at positions 3 and 4 of the piperidine ring is each R.

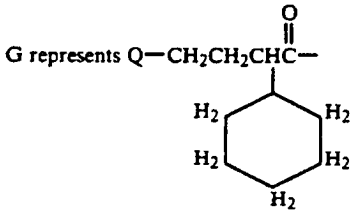
* * * * *

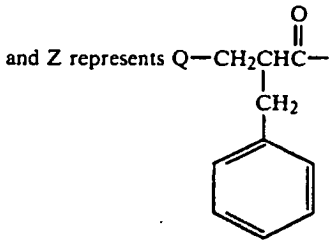
Claim 11 reads as follows:

11. [As corrected by Certificate of Correction] The compound of claim 1 selected from the group consisting of
$QCH_2CH[CH_2(C_6H_5)]C(O)OH$, $QCH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)$-$OCH_2CH_3$, $QCH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)OH$, Q-$CH_2CH_2CH$-

$(C_6H_5)C(O)NHCH_2C(O)NHCH_3$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)$-$NHCH_2CH_3$, G-$NH(CH_2)_2C(O)NH_2$, G-$NH(CH_2)_2C(O)NHCH_3$, G-$NHCH_2C(O)NH_2$, G-$NHCH_2C(O)NHCH_3$, G-$NHCH_2C(O)NHCH_2CH_3$, G-$NH(CH_2)_3C(O)OCH_2CH_3$, G-$NH(CH_2)_3C(O)NHCH_3$, G-$NH(CH_2)_2C(O)$-OH, G-$NH(CH_2)_3C(O)OH$, $QCH_2CH[CH_2\ (C_6H_{11})]C(O)NHCH_2C(O)OH$, $QCH_2CH[CH_2\ (C_6H_{11})]C(O)NH(CH_2)_2C(O)OH$, $QCH_2CH[CH_2\ (C_6H_{11})]$-$C(O)NH(CH_2)_2C(O)NH_2$, Z-$NHCH_2C(O)OCH_2CH_3$, Z-$NHCH_2C(O)OH$, Z-$NHCH_2C(O)NH_2$, Z-$NHCH_2C(O)N(CH_3)_2$, Z-$NHCH_2C(O)NHCH(CH_3)_2$, Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, Z-$NH(CH_2)_2C(O)OCH_2\ (C_6H_5)$, Z-NH-$(CH_2)_2C(O)OH$, Z-$NH(CH_2)_2C(O)NHCH_2CH_3$, Z-$NH(CH_2)_3C(O)NHCH_3$, Z-$NHCH_2C(O)NHCH_2C(O)OH$, Z-$NHCH_2C(O)OCH_2C(O)OCH_3$, Z-$NHCH_2$–$C(O)O(CH_2)_4CH_3$, Z-$NHCH_2C(O)OCH_2C(O)NHCH_3$, Z-$NHCH_2C(O)O$-(4-methoxycyclohexyl), Z-$NHCH_2C(O)OCH_2C(O)NHCH_2(C_6H_5)$, and Z-$NHCH_2C(O)OCH(CH_3)OC(O)CH_3$, wherein:







and pharmaceutically acceptable salts thereof.

Claim 11 is dependent on claim 1 and reads on (encompasses) the approved product for the reasons stated above, and more specifically when:

The selected compound is Z-$NHCH_2C(O)OH$.

* * * * *

Claim 12 reads as follows:

12. A compound of claim 11 selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)Z-$NHCH_2C(O)OH$, (—)Z-$NHCH_2C(O)OH$, (3R,4R,R)-$ZNHCH_2C(O)$-$OCH_2CH(CH_3)_2$, (3S,4S,S)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3R,4R)-$ZNHCH_2C(O)NHCH_2$ (C_6H_5) and (3R,4R)-G-$NH(CH_2)_3C(O)OH$, and pharmaceutically acceptable salts thereof.

Claim 12 is dependent on claim 11 and reads on (encompasses) the approved product for the reasons stated above, and more specifically when:

The selected compound is (+)Z-$NHCH_2C(O)OH$.

* * * * *

Claim 13 reads as follows:

13. A substantially pure stereoisomer of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

Claim 13 is dependent on claim 1 and reads on (encompasses) the approved product for the reasons stated above, and more specifically:

As stated in Section 11 "Description" of the Approved Label at lines 2-4, "alvimopan is the single sterioisomer [[2(S)-[[4(R)-(3-hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate."

* * * * *

Claim 14 reads as follows:

14. A pharmaceutical formulation comprising a compound of claim 1 or the salt thereof in combination with a pharmaceutically acceptable excipient.

Claim 14 is dependent on claim 1 and reads on (encompasses) the approved product for the reasons stated above, and more specifically when:

As stated in Section 11 "Description" of the Approved Label at lines 11-12, "ENTEREG Capsules for oral administration contain 12 mg of alvimopan on an anhydrous basis suspended in the inactive ingredient polyethylene glycol."

* * * * *

Claim 15 reads as follows:

15. A pharmaceutical formulation comprising a compound of claim 11 or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable excipient.

Claim 15 is dependent on claim 11 and reads on (encompasses) the approved product for the reasons stated above, and more specifically when:

As stated in Section 11 "Description" of the Approved Label at lines 11-12, "ENTEREG Capsules for oral administration contain 12 mg of alvimopan on an anhydrous basis suspended in the inactive ingredient polyethylene glycol."

* * * * *

Patent Claims to the Method of Using the Approved Product:

Method claims 17, 19 and 29-35 of U.S. Patent No. 5,250,542 encompass (read on) the approved product.

Claim 17 reads as follows:

17. A method for binding a peripheral opioid receptor in a patient which comprises administering to said patient an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

Method claim 17 is dependent on product claim 1, and reads on (encompasses) the approved product for the reasons stated with respect to claim 1 and additionally:

As stated in Section 11 "Description" of the Approved Label at lines 1-2, "ENTEREG Capsules contain alvimopan, a peripherally-acting μ-opioid receptor (PAM-OR) antagonist." The Approved Label additionally notes in Section 12.1 "Mechanism of Action" at lines 19-21, that "[f]ollowing oral administration, alvimopan antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion by competitively binding to gastrointestinal tract μ-opioid receptors."

* * * * *

Claim 19 reads as follows:

19. A method for blocking mu receptors in mammals comprising administering to a mammal requiring blocking of a mu receptor a receptor blocking dose of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

Method claim 19 is dependent on product claim 1, and reads on (encompasses) the approved product for the reasons stated with respect to claim 1 and additionally:

As stated in Section 11 "Description" of the Approved Label at lines 1-2, "ENTEREG Capsules contain alvimopan, a peripherally-acting μ-opioid receptor (PAM-OR) antagonist." The Approved Label additionally notes in Section 12.1 "Mechanism of Action" at lines 19-21, that "[f]ollowing oral administration, alvimopan antagonizes [*i.e.*, blocks] the peripheral effects of opioids on gastrointestinal motility and secretion by competitively binding to gastrointestinal tract μ-opioid receptors."

* * * * *

Claim 29 reads as follows:

29. A method for binding a peripheral opioid receptor in a patient which comprises administering to said patient an effective amount of a compound of claim 11.

Method claim 29 is dependent on product claim 11 and reads on (encompasses) the approved product for the reasons stated with respect to claim 11, and additionally:

As stated in Section 11 "Description" of the Approved Label at lines 1-2, "ENTEREG Capsules contain alvimopan, a peripherally-acting μ-opioid receptor (PAM-OR) antagonist." The Approved Label additionally notes in Section 12.1 "Mechanism of Action" at lines 19-21, that "[f]ollowing oral administration, alvimopan antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion by competitively binding to gastrointestinal tract μ-opioid receptors."

* * * * *

Claim 30 reads as follows:

30. A method of claim 29 wherein the compound is one selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)Z-$NHCH_2C(O)OH$, (—)Z-$NHCH_2C(O)OH$, (3R,4R,R)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,S)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-$ZNHCH_2C(O)OCH_2CH$-$(CH_3)_2$, (3R,4R)-$ZNHCH_2C(O)NHCH_2(C_6H_5)$ and (3R,4R)-G-$NH(CH_2)_3C(O)OH$.

Method claim 30 is dependent on method claim 29, which in turn is dependent on product claim 11, and reads on (encompasses) the approved product for the reasons stated with respect to claims 11 and 29, and more specifically when:

The selected compound is Z-$NHCH_2C(O)OH$ (*i.e.*, (+)Z-$NHCH_2C(O)OH$).

* * * * *

Claim 31 reads as follows:

31. A method of claim 19 wherein the compound is one wherein R^1 is hydrogen; R^2 is C_1–C_3 alkyl; n=1 or 2; and R^3 is benzyl, phenyl, cyclohexyl or cyclohexylmethyl.

Method claim 31 is dependent on method claim 19, which in turn is dependent on product claim 1, and reads on (encompasses) the approved product for the reasons stated with respect to claims 1 and 19, and more specifically when:

R^1 is hydrogen;

R^2 is a C_1-C_5 alkyl (*i.e.*, CH_3);

n is 1; and

R^3 is benzyl.

* * * * *

Claim 32 reads as follows:

32. A method of claim 31 wherein the compound is one wherein A is NR^5R^6 and R^5 is hydrogen, R^6 is $(CH_2)_q$ —B, q is 1 to 3 and B is —C(O)W.

Method claim 32 is dependent on method claim 31, which is dependent on method claim 19, which in turn is dependent on product claim 1, and reads on (encompasses) the approved product for the reasons stated with respect to claims 1, 19 and 31, and more specifically when:

A is NR^5R^6;

R^5 is hydrogen;

R^6 is $(CH_2)_q$–B;

q is 1; and

B is 

* * * * *

Claim 33 reads as follows:

33. A method of claim 32 wherein the compound is one wherein W is OR^9 and R^9 is hydrogen, C_1–C_5 alkyl, phenyl-substituted C_1–C_2 alkyl, C_5–C_6 cycloalkyl, or C_5–C_6 cycloalkyl-substituted C_1–C_3 alkyl.

Method claim 33 is dependent on method claim 32, which is dependent on method claim 31, which is dependent on method claim 19, which in turn is dependent on product claim 1, and reads on (encompasses) the approved product for the reasons stated with respect to claims 1, 19, 31 and 32, and more specifically when:

W is OR^9;

R^9 is hydrogen.

* * * * *

Claim 34 reads as follows:

34. A method for blocking a mu receptor in a mammal comprising administering to a mammal requiring blocking of a mu receptor a receptor blocking dose of a compound of claim 11.

Method claim 34 is dependent on product claim 11 and reads on (encompasses) the approved product for the reasons stated with respect to claim 11, and additionally:

As stated in Section 11 "Description" of the Approved Label at lines 1-2, "ENTEREG Capsules contain alvimopan, a peripherally-acting μ-opioid receptor (PAM-OR) antagonist." The Approved Label additionally notes in Section 12.1 "Mechanism of Action" at lines 19-21, that "[f]ollowing oral administration, alvimopan antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion by competitively binding to gastrointestinal tract μ-opioid receptors."

* * * * *

Claim 35 reads as follows:

35. A method of claim 34 wherein the compound is one selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)Z-$NHCH_2C(O)OH$, (—)Z-$NHCH_2C(O)OH$, (3R,4R,R)-

$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,S)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-$ZNHCH_2C(O)OCH_2$–$CH(CH_3)_2$, (3R,4R)-$ZNHCH_2C(O)NHCH_2(C_6H_5)$ and (3R,4R)-G-$NH(CH_2)_3C(O)OH$.

Method claim 35 is dependent on method claim 34, which in turn is dependent on product claim 11, and reads on (encompasses) the approved product for the reasons stated with respect to claims 11 and 34, and more specifically when: The selected compound is Z-$NHCH_2C(O)OH$ (*i.e.*, (+)Z-$NHCH_2C(O)OH$).

* * * * *

Patent Claims to the Method of Manufacturing the Approved Product:

No claims of U.S. Patent No. 5,250,542 are directed toward a method of manufacturing the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

The IND application for LY246736 Dihydrate Capsules was submitted to the FDA by Eli Lilly on October 11, 1993. By letter dated October 18, 1993, the FDA acknowledged receipt of the IND application on October 12, 1993, and assigned IND number 43,693, resulting in an IND effective date of November 11, 1993. A copy of this FDA acknowledgment letter is attached as **Exhibit 6**.

On November 5, 1996, Eli Lilly entered into a License Agreement with Roberts Laboratories Inc., a wholly owned subsidiary of Roberts Pharmaceutical Corporation (hereinafter collectively referred to as "Roberts"), granting Roberts the exclusive right to develop and commercialize LY246736, including a license under U.S. Patent 5,250,542. Effective February 1, 1997, Eli Lilly transferred sole sponsorship of IND 43,693 to Roberts, and notified the FDA by letter of February 3, 1997, a copy of which is attached as **Exhibit 7**.

On June 10, 1998, Adolor entered into an option and license agreement with Roberts (now Shire Pharmaceutical Group) under which Adolor is exclusively sublicensed to all rights of Shire with respect to LY246736, including a sublicense under U.S. Patent 5,250,542. On August 3, 1998, Adolor filed an IND application for the investigational drug ADL 8-2698 (Adolor's name for LY246736), which was assigned IND number 56,553. By letters dated June 24, 1998 and June 17, 1999, Roberts authorized the FDA to refer to IND 43,693 on behalf of Adolor Corporation (copies attached as **Exhibits 8 and 9**), and by letter to the FDA dated March 22, 2000, Roberts transferred all rights to IND 43,693 to Adolor (copy attached as **Exhibit 10**). Prior to this transfer on March 22, 2000,

Roberts withdrew IND 43,693 by letter to the FDA of December 3, 1999, noting that the investigational drug has been licensed to Adolor Corporation, and will be researched under the Adolor Corporation's IND application. By letter dated September 21, 2000 (copy attached as **Exhibit 11**), Adolor provided the FDA with requested information regarding the transfer of sponsorship of IND 43,693 from Roberts to Adolor on March 22, 2000, noting that the investigational compound LY236736 Dihydrate Capsules was licensed to Adolor for development, that Adolor filed its own IND 56,553, that Adolor's IND 56,553 was currently active and refers to the investigational drug as ADL 8-2698, that Roberts' (formerly Lilly's) IND 43,693 was referenced in Adolor's IND filing, and that any relevant sections and reports from IND 43,693 will be filed in the NDA.

Thus, although Adolor has conducted all clinical studies under IND 56,553, Adolor has used IND 43,693 as reference, and has submitted relevant sections and reports from IND 43,693 in the NDA. Under these circumstances, the "regulatory review period" under 35 U.S.C. § 156(g)(1) began on **November 11, 1993**, the effective date of IND 43,693.

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

The final reviewable unit constituting the complete NDA 21,775 for ENTEREG® was initially submitted to the FDA on June 25, 2004. The FDA acknowledged that the final reviewable unit of the complete NDA was received on June 25, 2004, as confirmed by the FDA letter dated September 7, 2004 (copy attached as **Exhibit 12**). This establishes June 25, 2004 as the initial submission date of the NDA for the approved product for purposes of 35 U.S.C. 156(g)(1).

(C) The date on which the NDA was approved or the Product License issued.

The NDA was approved by the FDA approval letter sent May 20, 2008, setting the effective date of the approval as the May 20, 2008 date of the letter. A copy of this five-page FDA approval letter plus the dated electronic signature page is attached as **Exhibit 13.** This establishes the end of the "regulatory review period" under 35 U.S.C. 156(g)(1) as May 20, 2008.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The significant activities undertaken by the marketing applicant with respect to the approved product during the applicable regulatory review period commenced with the submission by Lilly of an Investigational New Drug Application (IND) on October 11, 1993 for Compound LY246736 Dihydrate Capsules, which was assigned IND number 43,693. As detailed in answer to question (10)(i)(A) above, on November 5, 1996, Lilly entered into an agreement with Roberts, granting Roberts the rights to development of LY246736 Dihydrate Capsules. Effective February 1, 1997, Lilly transferred sole sponsorship of IND 43,693 to Roberts, and so notified the FDA by letter of February 3, 1997. By agreement dated June 10, 1998, Adolor entered into an Option and License Agreement with Roberts for a sublicense of all rights to the development and commercialization of LY246736, and on August 3, 1998, Adolor filed an IND application for the investigational drug ADL 8-2698 (Adolor's name for LY246736), which was assigned IND number 56,553. By letters dated June 24, 1998 and June 17, 1999, Roberts authorized the FDA to refer to IND 43,693 on behalf of Adolor Corporation, and by letter of dated March 22, 2000, Roberts transferred all rights to IND 43,693 to Adolor. Prior to this transfer on March 22, 2000, Roberts withdrew IND 43,693 by letter to the FDA of December 3, 1999, noting that the investigational drug has been licensed to Adolor, and will be researched under Adolor's IND application. Adolor's letter to the FDA of September 21, 2000, provided further information on the transfer of sponsorship of IND 43,693 from Roberts to Adolor on March 22, 2000, and made clear that LY236736 Dihydrate Capsules had been licensed to Adolor for development, that Adolor filed its own IND 56,553, that Adolor's IND 56,553 was currently active and refers to the investigational drug as ADL 8-2698, that IND 43,693 was referenced in Adolor's IND filing, and that any relevant sections and reports from IND 43,693 will be filed in the NDA. Although Adolor has conducted all clinical

studies under IND 56,553, Adolor has used IND 43,693 as reference, and has submitted relevant sections and reports from IND 43,693 in NDA 21,775.

Because of the complexities created by the circumstances and filings surrounding the transfers of IND 43,693, rights of reference thereto, and rights to the underlying compound LY245736 (ADL 8-2698 and later alvimopan) from Lilly to Roberts and then to Adolor, and the overlapping time period of studies done by Adolor under its IND 56,553, a Chronological Listing of Significant Activities during the testing phase under these two INDs and during the approval phase under NDA 21,775 is attached as **Exhibit 14**, the contents of which are incorporated herein by reference as providing a brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the Approved Product.

The regulatory review period for ENTEREG® (alvimopan) Capsules ended with permission for commercial marketing being granted by the FDA on May 20, 2008.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

Statement That The Patent Is Eligible For Extension

Applicant is of the opinion that U.S. Patent No. 5,250,542 is eligible for extension under 35 U.S.C. 156(a) because it satisfies all of the requirements for such extension as follows:

(1) 35 U.S.C. 156(a)

U.S. Patent No. 5,250,542 claims the approved product, as detailed in section (9) above.

(2) 35 U.S.C. 156(a)(1)

U.S. Patent No. 5,250,542 granted on an earliest filed U.S. application filed on March 29, 1991 and there are no terminal disclaimers. As such, the patent expires on March 29, 2011. This application, therefore, has been submitted before the expiration of the patent term.

(3) 35 U.S.C. 156(a)(2)

The term of this patent has never been extended.

(4) 35 U.S.C. 156(a)(3)

This application is being submitted by Eli Lilly and Company as the owner of record of No. 5,250,542 (through an assignment from the inventors recorded July 1, 1993 at Reel 006585, Frame 364), in accordance with the requirement of 35 U.S.C. 156(d) and rules of the U.S. Patent and Trademark Office.

(5) 35 U.S.C. 156(a)(4)

As evidenced by the May 20, 2008 approval letter from the FDA (**Exhibit 13**), ENTEREG® (alvimopan) Capsules was subject to a regulatory review period under Section 505(b) of the Federal Food, Drug, and Cosmetic Act before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)

The permission for commercial marketing of ENTEREG® (alvimopan) Capsules after this regulatory review period is the first permitted commercial marketing of ENTEREG® (alvimopan) Capsules under provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) under which the regulatory review period occurred, as confirmed by the absence of any approved NDA for the approved product prior to May 20, 2008.

(7) 35 U.S.C. 156(c)(4)

No other patent has been extended for the same regulatory review period for the product ENTEREG® (alvimopan) Capsules.

Statement as to Length of Extension Claimed

The term of U.S. Patent No. 5,250,542 should be extended by **1827 days**, from March 29, 2011 to **March 29, 2016**. In accordance with the implementing regulations of 37 C.F.R. 1.175 with respect to patent term extensions for a human drug product, the term extension of U.S. Patent No. 5,250,542 based on the regulatory review for ENTEREG® was determined as follows:

Sec. 1.775 Calculation of patent term extension for a human drug, antibiotic drug or human biological product.

(a) If a determination is made pursuant to Sec. 1.750 that a patent for a human drug, antibiotic drug or human biological product is eligible for extension, the term shall be extended by the time as calculated in days in the manner indicated by this section. The patent term extension will run from the original expiration date of the patent

or any earlier date set by terminal disclaimer (Sec. 1.321).

U.S. Patent 5,250,542 issued on October 5, 1993, from an earliest filed U.S. application filed on March 29, 1991. Pursuant to 35 U.S.C. 154(c), this patent is entitled to an original term of 20 years from March 29, 1991, which provides an original expiration date of **March 29, 2011**.

> **(b) The term of the patent for a human drug, antibiotic drug or human biological product will be extended by the length of the regulatory review period for the product as determined by the Secretary of Health and Human Services, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of this section.**
>
> **(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(1)(B), it is the sum of--**
>
> **(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act; and**
>
> **(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.**

The number of days in the IND testing period of paragraph (c)(1) extends from the effective date of IND 43,693 on November 11, 1993 to the filing of NDA 21,775 on June 25, 2004, being **3880 days**.

The number of days in the NDA approval period of paragraph (c)(2) extends from the filing of NDA 21,775 on June 25, 2004 to the date of approval of NDA 21,775 on May 20, 2008, being **1426 days**.

The regulatory review period is the sum of the periods of paragraphs (c)(1) and (c)(2), being **5306 days**.

> **(d) The term of the patent as extended for a human drug, antibiotic**

drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1) (i) and (ii) of this section; half days will be ignored for purposes of subtraction;

With respect to paragraph (d)(1)(i), **0 days** of the periods of paragraphs (c)(1) and (c)(2) were before the October 5, 1993 date on which original U.S. Patent 5,250,542 issued.

With respect to paragraph (d)(1)(ii), 35 U.S.C. 156(d)(2)(B) provides that if a petition is submitted to the Secretary not later than 180 days after publication of the determination of the applicable regulatory review period, upon which it may reasonably be determined that the applicant did not act with due diligence during the applicable regulatory review period, the Secretary shall determine if the applicant acted with due diligence during the applicable regulatory review period. The Secretary making this determination shall notify the Director of the determination and shall publish in the Federal Register a notice of such determination together with the factual and legal basis for such determination. Any interested person may request, within the 60-day period beginning on the publication of a determination, the Secretary to hold an informal hearing on the determination. If such a request is made within such period, the Secretary shall hold such hearing, and shall provide notice of the hearing to the owner of the patent involved and to any interested person and provide the owner and any interested person an opportunity to participate in the hearing. Within 30 days after the completion of the hearing, the Secretary shall affirm or revise the

determination which was the subject of the hearing and shall notify the Director of any revision of the determination and shall publish any such revision in the Federal Register. There has been no such petition or determination by the Secretary, and thus the number of days under (d)(1)(ii) is **0 days**.

With respect to paragraph (d)(1)(iii), one-half of the number of days remaining in the period defined by paragraph (c)(1) after that period is reduced in accordance with paragraphs (d)(1) (i) and (ii) is one-half of (3880-0-0=3880) days, which is **1940 days** (ignoring the half day).

Subtracting from the regulatory review period of 5306 days as determined above pursuant to section 1.175(c) the number of days determined above with respect to paragraphs (d)(1)(i), (ii) and (iii), the term of patent extension is **5306 days** minus **0 days** minus **0 days** minus **1940 days** for a sum total of **3366 days**.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

The original term of U.S. Patent No. 5,250,542 is March 29, 2011 and is not shortened by terminal disclaimer. Adding the 3366 days determined in paragraph (d)(1) to the original term of the patent results in an extended term to **June 15, 2020.**

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to the May 20, 2008 date of the approval of the NDA results in the date **May 20, 2022**.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier of June 15, 2020 and May 20, 2022 is **June 15, 2020**.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

The original patent issued after September 24, 1984. Adding 5 years to the original expiration date of the patent (there was no terminal disclaimer) of March 29, 2011 gives a date of **March 29, 2016**. The earlier of June 15, 2020 and March 29, 2016 is **March 29, 2016**.

(6) If the original patent was issued before September 24, 1984, and

(i) If no request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act before September 24, 1984, by--

(A) Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and

(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(i)(A) of this section with each other and selecting the earlier date; or

(ii) If a request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by--

(A) Adding 2 years to the original expiration date of the patent or earlier date set by terminal disclaimer, and

(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(ii)(A) of this section with each other and selecting the earlier date.

Since U.S. Patent 5,250,542 issued after September 24, 1984, no further adjustment to the extended term of March 29, 2016 is required.

Thus, as calculated above, the term of U.S. Patent No. 5,250,542 is eligible for a **1827 day extension to March 29, 2016**.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see § 1.765).

Applicant acknowledges a duty to disclose to the Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (see § 1.20(j)).

As noted in the letter of transmittal submitted with this application, the Patent and Trademark Office is authorized to charge the filing fee of $1,120.00 and any additional fees which may be required by this or any other related paper, or to credit any overpayment to Deposit Account No. 50-0310.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please address all inquiries and correspondence relating to this application for patent term extension to the following registered practitioner, who is counsel for the marketing applicant and authorized to act on behalf of the patent owner with respect to this Application and all correspondence pertaining hereto:

Donald J. Bird
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Telephone: 202-739-5320
Facsimile: 202-739-3001

A copy of the Authorization to Act is attached as **Exhibit 15**.

Respectfully Submitted,
Morgan, Lewis & Bockius LLP

Date: June 17, 2008 By: _____

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DJB:

LIST OF EXHIBITS

Exhibit No.	Ref. Pages	Description
1	2	US PTO Assignment of Cantrell Patent from inventors to Eli Lilly, recorded July 1, 1993 at Reel 006585, Frame 0364.
2	3	Approved Label for ENTEREG™ (alvimopan) capsules.
3	5	U.S. Patent No.5,250,542 to Cantrell et al.
4	5	Certificates of Correction issued December 28, 1999 and June 26, 2007 in U.S. Patent No. 5,250,542 to Cantrell et al.
5	5	Maintenance Fee Statement as of June 2, 2008 in U.S. Patent No. 5,250,542 to Cantrell et al., showing that all maintenance fees have been paid.
6	19	FDA letter dated October 18, 1993 acknowledging receipt of IND application on October 12, 1993, and assigning IND number 43,693.
7	19	Eli Lilly Letter of February 3, 1997 notifying FDA of transfer of sole sponsorship of IND 43,693 to Roberts, effective February 1, 1997
8	19	Roberts letter dated June 24, 1998 authorizing FDA to refer to IND 43,693 on behalf of Adolor Corporation.
9	19	Roberts letter dated June 17, 1999 authorizing FDA to refer to IND 43,693 on behalf of Adolor Corporation.
10	19	Roberts letter dated March 22, 2000 notifying FDA of transfer of all rights to IND 43,693 to Adolor.
11	20	Adolor letter dated September 21, 2000 providing FDA with requested information regarding the transfer of sponsorship of IND 43,693 from Roberts to Adolor.
12	20	FDA letter dated September 7, 2004 acknowledging receipt of the final reviewable unit constituting the complete Adolor NDA on June 25, 2004.
13	21, 25	Five-page FDA approval letter (with dated electronic signature page) under NDA Number 21,775 dated May 20, 2008.
14	23	Chronological Listing of Significant Activities under IND 43,693, IND 56,553 and NDA 21,775.
15	31	Authorization to Act on Behalf of Assignee-Patent Owner.

EXHIBIT 1

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 5250542 **Issue Dt:** 10/05/1993 **Application #:** 07916783 **Filing Dt:** 07/17/1992

Inventors: BUDDY E. CANTRELL, DENNIS M. ZIMMERMAN

Title: PERIPHERALLY SELECTIVE PIPERIDINE CARBOXYLATE OPIOID ANTAGONISTS

Assignment: 1

Reel/Frame: 006585/0364 **Recorded:** 07/01/1993 **Pages:** 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: CANTRELL, BUDDY E. **Exec Dt:** 03/29/1991

ZIMMERMAN, DENNIS M. **Exec Dt:** 03/29/1991

Assignee: ELI LILLY AND COMPANY
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LILLY CORPORATE CENTER
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Correspondent: MACHARRI R. VORNDRAN-JONES
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INDIANAPOLIS, IN 46285

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Web interface last modified: April 20, 2007 v.2.0.1

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RECORDATION FORM COVER SHEET
PATENTS ONLY **Attny Docket No. X-8244A**

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original document or copy thereof.

1. Name of conveying party(ies):

Buddy E. Cantrell
Dennis M. Zimmerman

Additional name(s) of conveying party(ies) attached? ( ) Yes (X) No

2. Name & address of receiving party(ies):

Name: Eli Lilly and Company

Internal Address: Patent Division/MVJ

Street Address: Lilly Corporate Center

City: Indianapolis State: IN Zip: 46285

3. Nature of conveyance:

(X) Assignment ( ) Merger
( ) Security Agreement ( ) Change of Name
( ) Other_____
Execution Date: March 29, 1991

Additional name(s) & address(es) attached?

( ) Yes (X) No

4. Application number(s) or patent Number(s):

If this document is being filed together with a new application, the execution date of the application is:_____

A. Patent Application No.(s): 07/916,783

B. Patent No.(s):

Additional Numbers attached ( ) Yes (X) No

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ASSIGNMENT BRANCH

5. Name and address of party to whom correspondance concerning documents should be mailed:

MaCharri R. Vorndran-Jones
Eli Lilly and Company/MVJ
Lilly Corporate Center
Indianapolis, IN 46285

6. Total number of applications and patents involved: 1 (1)

7. Total fee (37 CFR 3.41) $40.00
($40.00 per assignment)

( ) Enclosed
(X) Authorized to be charged to deposit account

8. Deposit account number: 05-0830

(attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

MaCharri R. Vorndran-Jones — MaCharri R. Vorndran-Jones — 6/28/93
Attorney Signing — Signature — Date

jaj

Total number of pages comprising cover sheet: (2)

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date appearing below.

ELI LILLY AND COMPANY
DF11001 07/09/93 07916783 05-0830 110 581 40.00CH

BY Cheryl J. Boyd DATE 6-28-93

REEL 6585 FRAME 364

ASSIGNMENT

Docket No. X-[illegible]

Whereas, we Buddy E. Cantrell, City of Fountaintown, County of Hancock and Dennis M. Zimmerman, City of Mooresville, County of Hendricks; both the State of Indiana.

have made an invention which is the subject of an application for Letters Patent of the United States ("Application") entitled Peripherally Selective Piperidine Carboxylate Opioid Antagonists

which has been executed by us on the 29th day of March, 19 91; and

Whereas ELI LILLY AND COMPANY, an Indiana corporation having its principal place of business at LILLY CORPORATE CENTER, Indianapolis, Indiana 46285, wishes to acquire the entire interest in all inventions disclosed in such Application;

Now, therefore, in consideration of the sum of one dollar ($1.00) and other good and valuable consideration, the receipt of which is hereby acknowledged, we hereby sell, assign, transfer and set over unto Eli Lilly and Company, its successors and assigns (collectively "Lilly") our entire right, title and interest in, to and under the Application, including all priority rights for other countries arising therefrom, all inventions therein disclosed, and any and all Letters Patent of the United States and of all other countries which may be granted for such inventions, or any of them, all such inventions and all rights in such Application and Letters Patent to be held and enjoyed by Lilly for its own use and enjoyment to the full end of the term or terms for which such Letters Patent may be granted, as fully and entirely as the same would have been held and enjoyed by us had this assignment and sale not been made.

We authorize and request the Commissioner of Patents and Trademarks of the United States to issue any such Letters Patent which may be granted on the Application to Lilly as assignee of the entire right, title and interest therein and thereto.

For ourselves and for our legal representatives, we covenant and agree with Lilly that we have not granted to any others any license to make, use or sell any of such inventions, that our right, title and interest in such inventions has not been encumbered, that we have good right and title to sell and assign the same, and that we will not execute any instrument in conflict herewith.

For ourselves and for our heirs, successors and legal representatives, we further covenant and agree with Lilly that upon request we and they will: (i) execute continuing, divisional, or reissue applications, amended specifications, or rightful declarations or oaths; (ii) communicate to Lilly any facts known to us or them relating to such inventions or the history thereof; (iii) execute preliminary statements and testify in any interference proceedings or litigation; (iv) execute and deliver any application papers, assignments, or other instruments; and (v) do all other acts which, in the opinion of counsel for Lilly, may be necessary or desirable to secure the grant of Letters Patent to Lilly or its nominees, in the United States and in all other countries where Lilly may desire to have such inventions, or any of them, patented, with specifications and claims in such form as shall be approved by counsel for Lilly and to vest and confirm in Lilly or its nominees the full and complete legal and equitable title to all such Letters Patent, without further consideration than that now paid but at the expense of Lilly.

In Witness Whereof we have executed this assignment on the 29th day of March 19 91

Buddy E. Cantrell
Buddy E. Cantrell

Dennis M. Zimmerman
Dennis M. Zimmerman

RECORDED
PATENT AND TRADEMARK
OFFICE
JUL 1 1993

NEIL 6505 FRAME 365

UNITED STATES OF AMERICA

State of Indiana
County of Hendricks } ss. March 29 1991

Before me, a Notary Public for Hendricks County, State of Indiana, personally appeared Buddy E. Cantrell and Dennis M. Zimmerman and acknowledged the execution of the foregoing instrument this 29th day of March, 19 91

Elizabeth A. Stoneking
My Commission Expires
September 25, 1993
Residence: Hendricks Co.

Elizabeth A Stoneking
Notary Public

EXHIBIT 2

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENTEREG safely and effectively. See full prescribing information for ENTEREG.

ENTEREG® (alvimopan) Capsules
Initial U.S. Approval: 2008

WARNING: FOR SHORT-TERM HOSPITAL USE ONLY

ENTEREG is available only for short-term (15 doses) use in hospitalized patients. Only hospitals that have registered in and met all of the requirements for the ENTEREG Access Support and Education (E.A.S.E.™) program may use ENTEREG.

INDICATIONS AND USAGE

ENTEREG is a peripherally acting μ-opioid receptor antagonist indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis. (1)

DOSAGE AND ADMINISTRATION

12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily for up to 7 days for a maximum of 15 doses. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 12 mg (3)

CONTRAINDICATIONS

Therapeutic doses of opioids for more than 7 consecutive days prior to ENTEREG (4)

WARNINGS AND PRECAUTIONS

- A higher number of myocardial infarctions was reported in patients treated with alvimopan 0.5 mg twice daily compared with placebo in a 12-month study in patients treated with opioids for chronic pain, although a causal relationship has not been established. (5.1)
- Patients recently exposed to opioids are expected to be more sensitive to the effects of ENTEREG and therefore may experience abdominal pain, nausea and vomiting, and diarrhea. (5.3)
- Not recommended in patients with severe hepatic impairment. (5.4)
- Not recommended in patients with end stage renal disease. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3% and ≥1% placebo) in patients undergoing bowel resection were anemia, dyspepsia, hypokalemia, back pain, and urinary retention. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Adolor Corporation at 1-866-4ADOLOR (1-866-423-6567) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Patients with mild-to-moderate hepatic impairment do not require dosage adjustment, but they should be monitored for adverse effects. ENTEREG is not recommended for patients with severe hepatic impairment.(8.5)
- Renal impairment: Alvimopan has not been studied in patients with end stage renal disease. ENTEREG is not recommended for use in these patients. Dosage adjustment is not required in patients with mild to severe renal impairment but they should be monitored for adverse effects. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: May 2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FOR SHORT-TERM HOSPITAL USE ONLY

ENTEREG is available only for short-term (15 doses) use in hospitalized patients. Only hospitals that have registered in and met all of the requirements for the ENTEREG Access Support and Education (E.A.S.E.) program may use ENTEREG. *[see Warnings and Precautions (5.1 and 5.2)]*

1 INDICATIONS AND USAGE

ENTEREG is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage in Adults

For hospital use only. The recommended adult dosage of ENTEREG is 12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily beginning the day after surgery for a maximum of 7 days or until discharge. Patients should not receive more than 15 doses of ENTEREG.

2.2 Special Populations

Geriatric Use: No dosage adjustment is necessary in elderly patients *[see Use in Specific Populations (8.4)]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild-to-moderate hepatic impairment (Child-Pugh Class A and B). ENTEREG is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)]*.

Renal Impairment: No dosage adjustment is necessary in patients with mild-to-severe renal impairment, but they should be monitored for adverse effects. ENTEREG is not recommended for use in patients with end-stage renal disease. *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

12 mg blue, hard gelatin capsules with "ADL2698" printed on both the body and the cap of the capsule.

4 CONTRAINDICATIONS

ENTEREG is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking ENTEREG.

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Infarction in a 12 Month Study in Patients treated with Opioids for Chronic Pain

There were more reports of myocardial infarctions in patients treated with alvimopan

0.5 mg twice daily compared with placebo-treated patients in a 12-month study of patients treated with opioids for chronic pain. In this study, the majority of myocardial infarctions occurred between 1 and 4 months after initiation of treatment. This imbalance has not been observed in other studies of alvimopan, including studies in patients undergoing bowel resection surgery who received alvimopan 12 mg twice daily for up to 7 days. A causal relationship with alvimopan has not been established.

5.2 Distribution Program for ENTEREG

ENTEREG is available only to hospitals that enroll in the E.A.S.E. program. To enroll in the E.A.S.E. program, the hospital must acknowledge that:

-hospital staff who prescribe, dispense, or administer ENTEREG have been provided the educational materials on the need to limit use of ENTEREG to short-term, inpatient use;
-patients will not receive more than 15 doses of alvimopan; and
-ENTEREG will not be dispensed to patients after they have been discharged from the hospital.

Contact the E.A.S.E. program at 1-866-4ADOLOR (1-866-423-6567).

5.3 Opioid Tolerance and Gastrointestinal-Related Adverse Effects

Patients recently exposed to opioids are expected to be more sensitive to the effects of μ-opioid receptor antagonists. Since ENTEREG acts peripherally, clinical signs and symptoms of increased sensitivity would likely be limited to the gastrointestinal tract (e.g., abdominal pain, nausea and vomiting, diarrhea). Patients receiving more than 3 doses of an opioid within the week prior to surgery were not studied in the postoperative ileus clinical trials; therefore, ENTEREG 12 mg capsules should be administered with caution to these patients.

5.4 Severe Hepatic Impairment

In patients with severe hepatic impairment, there is a potential for 10-fold higher plasma levels of drug *[see Clinical Pharmacology (12.3)]*. There are no studies of ENTEREG in patients with severe hepatic impairment undergoing bowel resection. Because of the limited data available, ENTEREG is not recommended for use in patients with severe hepatic impairment.

5.5 End-Stage Renal Disease

No studies have been conducted with end-stage renal disease. ENTEREG is not recommended for use in these patients.

5.6 Bowel Obstruction

Use of ENTEREG in patients undergoing surgery for correction of complete bowel obstruction is not recommended.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The adverse event information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to ENTEREG in 1,650 patients in 9 placebo-controlled studies worldwide. The population was 19 to 97 years old, 68% were female, and 83% were Caucasian; 61% were undergoing bowel resection surgery. The first dose of ENTEREG was administered 30 minutes to 5 hours before the scheduled start of surgery and then twice daily until hospital discharge (or for a maximum of 7 days of postoperative treatment).

Table 1 presents treatment-emergent adverse reactions reported in ≥3% patients treated with ENTEREG and for which the rate for ENTEREG was ≥1% than placebo. Treatment-emergent adverse reactions are those events occurring after the first dose of study medication treatment and within 7 days of the last dose of study medication or those events present at baseline that increased in severity after the start of study medication treatment.

Table 1. Treatment-Emergent Adverse Reactions That Were Reported in ≥3% of Either Bowel Resection Patients Treated With ENTEREG or All Surgical Patients Treated With ENTEREG and for Which the Rate for ENTEREG Was ≥1% Than Placebo

	Bowel Resection Patients		All Surgical Patients	
System Organ Class	Placebo (n = 986) %	ENTEREG (n = 999) %	Placebo (n = 1,365) %	ENTEREG (n = 1,650) %
Blood and lymphatic system disorders				
Anemia	4.2	5.2	5.4	5.4
Gastrointestinal disorders				
Constipation	3.9	4.0	7.6	9.7
Dyspepsia	4.6	7.0	4.8	5.9
Flatulence	4.5	3.1	7.7	8.7
Metabolism and nutrition disorders				
Hypokalemia	8.5	9.5	7.5	6.9
Musculoskeletal and connective tissue disorders				
Back pain	1.7	3.3	2.6	3.4
Renal and urinary disorders				
Urinary retention	2.1	3.2	2.3	3.5

7 DRUG INTERACTIONS

7.1 Potential for Drugs to Affect Alvimopan Pharmacokinetics

Based on *in vitro* data, alvimopan is not a substrate of CYP enzymes. Therefore, concomitant administration of ENTEREG with inducers or inhibitors of CYP enzymes is unlikely to alter the metabolism of alvimopan. No clinical studies have been performed to assess the effect of concomitant administration of inducers or inhibitors of cytochrome P450 enzymes on alvimopan pharmacokinetics.

In vitro studies suggest that alvimopan and its 'metabolite' are substrates for p-glycoprotein. A population PK analysis did not reveal any evidence that alvimopan or 'metabolite' pharmacokinetics were influenced by concomitant medications that are mild-to-moderate p-glycoprotein inhibitors. No clinical studies of concomitant administration of alvimopan and strong inhibitors of p-glycoprotein (e.g., verapamil, cyclosporine, amiodorone, itraconazole, quinine, spirinolactone, quinidine, diltiazem, bepridil) have been conducted.

A population PK analysis suggests that the pharmacokinetics of alvimopan were not affected by concomitant administration of acid blockers or antibiotics. However, plasma concentrations of the 'metabolite' were lower in patients receiving acid blockers or preoperative oral antibiotics (49% and 81%, respectively). Because the 'metabolite' is not required for efficacy, no dosage adjustments are necessary in these patients.

7.2 Potential for Alvimopan to Affect the Pharmacokinetics of Other Drugs

Alvimopan and its 'metabolite' are not inhibitors of CYP 1A2, 2C9, 2C19, 3A4, 2D6, and 2E1 *in vitro* at concentrations far in excess of those observed clinically. Alvimopan and its 'metabolite' are not inducers of CYP 1A2, 2B6, 2C9, 2C19 and 3A4. *In vitro* studies also suggest that alvimopan and its 'metabolite' are not inhibitors of p-glycoprotein. These *in vitro* findings suggest that ENTEREG is unlikely to alter the pharmacokinetics of coadministered drugs through inhibition or induction of CYP enzymes or inhibition of p-glycoprotein.

Coadministration of alvimopan does not appear to alter the pharmacokinetics of morphine and its metabolite, morphine-6-glucuronide, to a clinically significant degree when morphine is administered intravenously. Dosage adjustment for intravenously administered morphine is not necessary when it is coadministered with alvimopan.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in pregnant rats at about 68 to 136 times the recommended human oral dose based on the body surface area and intravenous doses of about 3.4 to 6.8 times the recommended human oral dose based on the body surface area and in pregnant rabbits at intravenous doses at about 5 to 10 times the recommended human oral dose based on the body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to alvimopan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Nursing Mothers

Alvimopan and its 'metabolite' are detected in the milk of lactating rats. It is not known whether alvimopan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ENTEREG is administered to a nursing woman.

8.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.4 Geriatric Use

Of the total number of patients in 5 clinical efficacy studies treated with ENTEREG or placebo, 45% were 65 years of age and over, while 18% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment based on increased age is required *[see Clinical Pharmacology (12.3)]*.

8.5 Hepatic Impairment

Although there is a potential for higher plasma levels of drug in patients with mild-to-moderate hepatic impairment *[see Clinical Pharmacology (12.3)]*, dosage adjustment in these patients is not required. Patients with mild-to-moderate hepatic impairment should be closely monitored for possible adverse effects (e.g., diarrhea, gastrointestinal pain, cramping) that could indicate high drug or 'metabolite' levels, and ENTEREG should be discontinued if adverse events occur. ENTEREG is not recommended for use in patients with severe hepatic impairment. *[See Dosage and Administration (2.2), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3)]*

8.6 Renal Impairment

Alvimopan has not been studied in patients with end-stage renal disease and ENTEREG is not recommended for use in these patients. Patients with mild-to-severe renal impairment do not require dosage adjustment, but they should be monitored for adverse effects. *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*. Patients with severe impairment should be closely monitored for possible adverse effects (e.g., diarrhea, gastrointestinal pain, cramping) that could indicate high drug or 'metabolite' levels, and ENTEREG should be discontinued if adverse events occur.

9 DRUG ABUSE AND DEPENDENCE

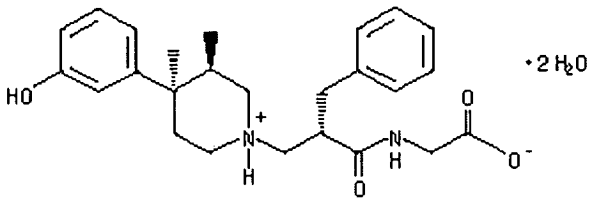
ENTEREG has no known potential for abuse or dependence.

10 OVERDOSAGE

There is no specific antidote for overdosage with ENTEREG. Patients should be managed with appropriate supportive therapy. Single doses up to 120 mg and multiple doses up to 48 mg for 7 days have been administered to normal, healthy subjects in clinical studies and were well tolerated.

11 DESCRIPTION

ENTEREG Capsules contain alvimopan, a peripherally-acting μ-opioid receptor (PAM-OR) antagonist. Chemically, alvimopan is the single stereoisomer [[2(S)-[[4(*R*)-(3-hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate. It has the following structural formula:



Alvimopan is a white to light beige powder with a molecular weight of 460.6, and the empirical formula is $C_{25}H_{32}N_2O_4 \bullet 2H_2O$. It has a solubility of <0.1 mg/mL in water or buffered solutions between pH 3.0 and 9.0, 1 to 5 mg/mL in buffered solutions at pH 1.2, and 10 to 25 mg/mL in aqueous 0.1 N sodium hydroxide. At physiological pH, alvimopan is zwitterionic, a property that contributes to its low solubility.

ENTEREG Capsules for oral administration contain 12 mg of alvimopan on an anhydrous basis suspended in the inactive ingredient polyethylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alvimopan is a selective antagonist of the cloned human μ-opioid receptor with a Ki of 0.4 nM (0.2 ng/mL) and no measurable opioid-agonist effects in standard pharmacologic assays. The dissociation of [^{3}H]-alvimopan from the human μ-opioid receptor is slower than that of other opioid ligands, consistent with its higher affinity for the receptor. At concentrations of 1 to 10 μM, alvimopan demonstrated no activity at any of over 70 non-opioid receptors, enzymes, and ion channels.

Postoperative ileus is the impairment of gastrointestinal motility after intra-abdominal surgery or other non-abdominal surgeries. Postoperative ileus affects all segments of the gastrointestinal tract and may last from 5 to 6 days, or even longer. This may potentially delay gastrointestinal recovery and hospital discharge until its resolution. It is characterized by abdominal distention and bloating, nausea, vomiting, pain, accumulation of gas and fluids in the bowel, and delayed passage of flatus and defecation. Postoperative ileus is the result of a multifactorial process that includes inhibitory sympathetic input, release of hormones, neurotransmitters, and other mediators (e.g., endogenous opioids). A component of postoperative ileus also results from an inflammatory reaction and the effects of opioid analgesics. Morphine and other μ-opioid receptor agonists are universally used for the treatment of acute postsurgical pain; however, they are known to have an inhibitory effect on gastrointestinal motility and may prolong the duration of postoperative ileus.

Following oral administration, alvimopan antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion by competitively binding to gastrointestinal tract μ-opioid receptors. The antagonism produced by alvimopan at opioid receptors is evident in isolated guinea pig ileum preparations where alvimopan competitively antagonizes the effects of morphine on contractility. Alvimopan achieves this selective gastrointestinal opioid antagonism without reversing the central analgesic effects of μ-opioid agonists.

12.2 Pharmacodynamics

In exploratory studies in healthy volunteers, alvimopan 3 mg three times daily appeared to reduce the delay in gastrointestinal transit produced by morphine 30 mg twice daily as measured by radio-opaque markers.

In a study designed to evaluate potential effects on cardiac conduction, alvimopan did not cause clinically significant QTc prolongation at doses up to 24 mg twice daily for 7 days. The potential for QTc effects at higher doses has not been studied.

12.3 Pharmacokinetics

Following oral administration of alvimopan, an amide hydrolysis compound is present in the systemic circulation, which is considered a product exclusively of intestinal flora metabolism. This compound is referred to as the 'metabolite'. It is also a μ-opioid receptor antagonist with a Ki of 0.8 nM (0.3 ng/mL).

Absorption: Following oral administration of ENTEREG capsules in healthy volunteers, plasma alvimopan concentration peaked at approximately 2 hours postdose. No significant accumulation in alvimopan concentration was observed following twice daily (BID) dosing. The mean peak plasma concentration was 10.98 (±6.43) ng/mL and mean $AUC_{0\text{-}12h}$ was 40.2 (±22.5) ng•h/mL after dosing of alvimopan at 12 mg BID for 5 days. The absolute bioavailability was estimated to be 6% (range, 1% to 19%). Plasma concentrations of alvimopan increased approximately proportionally with increasing doses between 6 and 18 mg, but less than proportionally from 18 to 24 mg.

There was a delay in the appearance of the 'metabolite', which had a median T_{max} of 36 hours following administration of a single dose of alvimopan. Concentrations of the 'metabolite' were highly variable between subjects and within a subject. The 'metabolite' accumulated after multiple doses of ENTEREG. The mean C_{max} for the 'metabolite' after alvimopan 12 mg twice daily for 5 days was 35.73±35.29 ng/mL.

Concentrations of alvimopan and its metabolite are higher (~1.9-fold and ~1.4-fold, respectively) in POI patients than in healthy volunteers.

Food Effects: A high-fat meal decreased the extent and rate of alvimopan absorption. The C_{max} and AUC were decreased by approximately 38% and 21%, respectively, and the T_{max} was prolonged by approximately 1 hour. The clinical significance of this decreased bioavailability is unknown. In POI clinical trials, the preoperative dose of ENTEREG was administered in a fasting state. Subsequent doses were given without regard to meals.

Distribution: The steady state volume of distribution of alvimopan was estimated to be 30±10 L. Plasma protein binding of alvimopan and its 'metabolite' was independent of concentration over ranges observed clinically and averaged 80% and 94%, respectively. Both alvimopan and the 'metabolite' were bound to albumin and not to alpha-1 acid glycoprotein.

Metabolism and Elimination: The average plasma clearance for alvimopan was 402 (±89) mL/min. Renal excretion accounted for approximately 35% of total clearance. There was no evidence that hepatic metabolism was a significant route for alvimopan elimination. Biliary secretion was considered the primary pathway for alvimopan elimination. Unabsorbed drug and unchanged alvimopan resulting from biliary excretion were then hydrolyzed to its 'metabolite'

by gut microflora. The 'metabolite' was eliminated in the feces and in the urine as unchanged 'metabolite', the glucuronide conjugate of the 'metabolite', and other minor metabolites. The mean terminal phase half-life of alvimopan after multiple oral doses of ENTEREG ranged from 10 to17 hours. The terminal half-life of the 'metabolite' ranged 10 to 18 hours.

Special Populations:

Age: The pharmacokinetics of alvimopan, but not its 'metabolite', were related to age, but this effect was not clinically significant and does not warrant dosage adjustment based on increased age.

Race: The pharmacokinetic characteristics of alvimopan were not affected by race. Plasma 'metabolite' concentrations were lower in black and in Hispanic patients (by 43% and 82%, respectively) than in Caucasian patients following alvimopan administration. These changes are not considered to be clinically significant in surgical patients; therefore, dosage adjustment based on race is not required.

Gender: There was no effect of gender on the pharmacokinetics of alvimopan or the 'metabolite'.

Hepatic Impairment: Exposure to alvimopan following a single 12-mg dose tended to be higher (1.5 to 2 fold, on average) in patients with mild or moderate hepatic impairment (as defined by Child-Pugh Class A and B, n = 8 each) compared with healthy controls (n = 4). There were no consistent effects on the C_{max} or half-life of alvimopan in patients with hepatic impairment. However, two of 16 patients with mild to moderate impairment had longer than expected half-lives of alvimopan indicating that some accumulation may occur upon multiple dosing. The C_{max} of the 'metabolite' tended to be more variable in patients with mild or moderate hepatic impairment than in matched normal subjects. A study of 3 patients with severe hepatic impairment (Child-Pugh Class C), indicated similar alvimopan exposure in 2 patients and an approximately 10-fold increase in C_{max} and exposure in 1 patient with severe hepatic impairment when compared with healthy control volunteers *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.5)]*.

Renal Impairment: There was no relationship between renal function (i.e., creatinine clearance [CrCl]) and plasma alvimopan pharmacokinetics (C_{max}, AUC, or half-life) in patients with mild (CrCl 51-80 mL/min), moderate (CrCl 31-50 mL/min), or severe (CrCl <30 mL/min) renal impairment (n = 6 each). Renal clearance of alvimopan was related to renal function; however, because renal clearance was only a small fraction (35%) of the total clearance, renal impairment had a small effect on the apparent oral clearance of alvimopan. The half-lives of alvimopan were comparable in the mild, moderate and control renal impairment groups but longer in the severe renal impairment group. Exposure to the 'metabolite' tended to be 2- to 5-fold higher in patients with moderate or severe renal impairment compared to patients with mild renal impairment or control subjects. Thus, there may be accumulation of alvimopan and 'metabolite' in patients with severe renal impairment receiving multiple doses of ENTEREG. Patients with end-stage renal disease were not studied *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.6)]*.

Crohn's Disease: There was no relationship between disease activity in patients with Crohn's disease (measured as Crohn's Disease Activity Index or bowel movement frequency) and alvimopan pharmacokinetics (AUC or C_{max}). Patients with active or quiescent Crohn's disease had increased variability in alvimopan pharmacokinetics and exposure tended to be 2-fold higher in patients with quiescent disease than in those with active disease or normal subjects. Concentrations of the 'metabolite' were lower in patients with Crohn's disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two year carcinogenicity studies have been conducted with alvimopan in CD-1 mice at oral doses up to 4000 mg/kg/day and in Sprague Dawley rats at oral doses up to 500 mg/kg/day. Oral administration of alvimopan for 104 weeks produced significant increases in the incidences of fibroma, fibrosarcoma and sarcoma in the skin/subcutis, and osteoma/osteosarcoma in bones of female mice at 4000 mg/kg/day (about 674 times the recommended human dose based on body surface area). In rats, oral administration of alvimopan for 104 weeks did not produce any tumor up to 500 mg/kg/day (about 166 times the recommended human dose based on body surface area).

Alvimopan was not genotoxic in the Ames test, the mouse lymphoma cell ($L5178Y/TK^{+/-}$) forward mutation test, the Chinese Hamster Ovary (CHO) cell chromosome aberration test or the mouse micronucleus test. The pharmacologically active 'metabolite' ADL 08-0011 was negative in the Ames test, chromosome aberration test in CHO cells and mouse micronucleus test.

Alvimopan at intravenous doses up to 10 mg/kg/day (about 3.4 to 6.8 times the recommended human oral dose based on the body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

A single oral dose of 500 mg/kg of alvimopan was not lethal to mice and rats.

Reproduction studies have been performed in pregnant rats at oral doses up to 200 mg/kg/day (about 68 to 136 times the recommended human oral dose based on the body surface area) and intravenous doses up to 10 mg/kg/day (about 3.4 to 6.8 times the recommended human oral dose based on the body surface area) and in pregnant rabbits at intravenous doses up to 15 mg/kg/day (about 5 to 10 times the recommended human oral dose based on the body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to alvimopan.

14 CLINICAL STUDIES

14.1. Postoperative Ileus

The efficacy of ENTEREG in the management of postoperative ileus was evaluated in 5 multicenter, randomized, double-blind, parallel-group, placebo-controlled studies: 4 US studies (Studies 1-4) and 1 non-US study (Study 5). Patients 18 years of age or older undergoing partial large or small bowel resection surgery with primary anastomosis or total abdominal hysterectomy under general anesthesia were randomly assigned to receive oral doses of ENTEREG 12 mg or matching placebo. The initial dose was administered at least 30 minutes

and up to 5 hours prior to the scheduled start of surgery for most patients, and subsequent doses were administered twice daily beginning on the first postoperative day and continued until hospital discharge or a maximum of 7 days. There were no limitations on the type of general anesthesia used, but intrathecal or epidural opioids or anesthetics were prohibited.

All patients in the US studies were scheduled to receive intravenous patient-controlled opioid analgesia. In the non-US study, patients were scheduled to receive opioids either by intravenous patient-controlled opioid analgesia or bolus parenteral administration (intravenous or intramuscular). In all studies, there was no restriction on the type of opioid used or the duration of intravenous patient-controlled opioid analgesia. A standardized accelerated postoperative care pathway was implemented: early nasogastric tube removal (end of surgery); early ambulation (day following surgery); early diet advancement (liquids offered the day following surgery) and solids by the second day following surgery, as tolerated.

Patients who received more than 3 doses of an opioid (regardless of route) during the 7 days prior to surgery and patients with complete bowel obstruction or who were scheduled for a total colectomy, colostomy, or ileostomy were excluded.

The primary endpoint for all studies was time to achieve resolution of postoperative ileus, a clinically defined composite measure of both upper and lower gastrointestinal recovery. Although both 2-component (GI2: toleration of solid food and first bowel movement) and 3-component (GI3: toleration of solid food and either first flatus or bowel movement) endpoints were used in all studies, GI2 is presented as it represents the most objective and clinically relevant measure of treatment response in the bowel resection population. The time from the end of surgery to when the discharge order was written represented the length of hospital stay. In the 5 studies, 1,081 patients received placebo (157 for total abdominal hysterectomy) and 1,096 patients received ENTEREG (143 for total abdominal hysterectomy).

The efficacy of ENTEREG following total abdominal hysterectomy has not been established. Therefore, the following data are presented for the bowel resection population only.

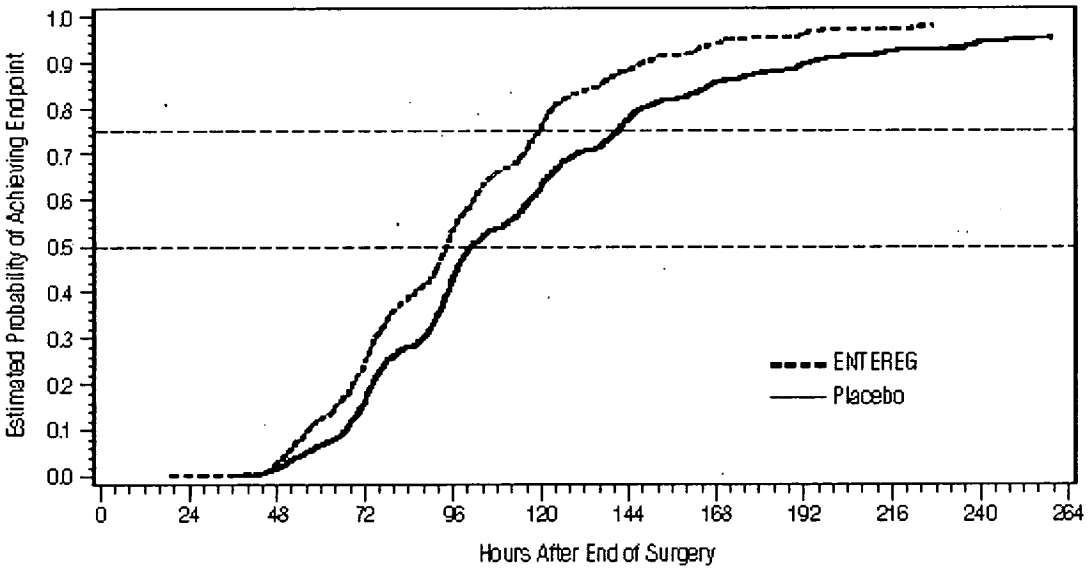
Bowel Resection: A total of 1,877 patients underwent bowel resection. The average age was 61 years with equal proportions of males and females, and 88% were Caucasian. The most common indications for surgery were colon or rectal cancer and diverticular disease. In the non-US study (Study 5), average daily postoperative opioid consumption was approximately 50% lower and the use of non-opioid analgesics substantially higher, as compared with the US studies (Studies 1-4) for both treatment groups. During the first 48 hours postoperatively, the use of non-opioid analgesics was 69% compared with 4% for the non-US and US studies, respectively. In each of the 5 studies, ENTEREG accelerated the time to recovery of gastrointestinal function, as measured by the composite endpoint GI2, and time to discharge order written as compared with placebo. Hazard ratios greater than 1 indicate a higher probability of achieving the event during the study period with treatment with ENTEREG than with placebo. Table 2 provides the Hazard Ratios, Kaplan Meier means and the mean treatment differences (hours) in gastrointestinal recovery between ENTEREG and placebo.

Table 2. GI2 Recovery (Hours) in Bowel Resection Patients

Study No.	ENTEREG 12 mg Mean	Placebo Mean	Treatment Difference Mean	Hazard Ratio (95% CI)
1	92.0	111.8	19.8	1.533 (1.293, 1.816)
2	105.9	132.0	26.1	1.625 (1.256, 2.102)
3	116.4	130.3	14.0	1.365 (1.057, 1.764)
4	106.7	119.9	13.2	1.400 (1.035, 1.894)
5	98.8	109.5	10.7	1.299 (1.070, 1.575)

Gastrointestinal recovery began after approximately 48 hours post surgery. The proportion of patients receiving ENTEREG who achieved GI2 was higher at all times throughout the study observation period compared with those receiving placebo (Figure 1).

Figure 1 Time to GI2 Based on the Combined Data from Five Studies



Across studies 1-4, patients receiving ENTEREG had their discharge order written approximately 13 to 21 hours sooner compared to patients receiving placebo.

ENTEREG did not reverse opioid analgesia as measured by visual analog scale pain

intensity scores and/or amount of postoperative opioids administered across all 5 studies.

There were no gender-, age-, or race-related differences in treatment effect.

The incidence of anastomotic leak was low and comparable in patients receiving either ENTEREG or placebo (0.8% and 1.1%, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

ENTEREG Capsules, 12 mg, are blue, hard-gelatin capsules printed with "ADL2698" on both the body and the cap of the capsule. ENTEREG Capsules are available in unit-dose packs of 30 capsules (30 doses) (NDC 11227-010-30) for hospital use only.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

17.1 Recent Use of Opioids

Patients should be informed that they must disclose long-term or intermittent opioid pain therapy, including any use of opioids in the week prior to receiving ENTEREG. They should understand that recent use of opioids may make them more susceptible to adverse reactions to ENTEREG, primarily those limited to the gastrointestinal tract (e.g., abdominal pain, nausea and vomiting, diarrhea).

17.2 Hospital Use Only

Patients should be informed that ENTEREG is for hospital use only for no more than 7 days after their bowel resection surgery.

17.3 Most Common Side Effects

Patients should be informed that the most common side effects with ENTEREG in patients undergoing bowel resection are constipation, dyspepsia, and flatulence.

Manufactured for Adolor Corporation
Exton, PA 19341-1127

Distributed by GlaxoSmithKline
Research Triangle Park, NC 27709

US Patent Nos. 5,250,542; 5,434,171; 6,469,030

EXHIBIT 3

US005250542A

United States Patent [19]

Cantrell et al.

[11] Patent Number: 5,250,542

[45] Date of Patent: Oct. 5, 1993

[54] PERIPHERALLY SELECTIVE PIPERIDINE CARBOXYLATE OPIOID ANTAGONISTS

[75] Inventors: **Buddy E. Cantrell**, Fountaintown; **Dennis M. Zimmerman**, Mooresville, both of Ind.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[21] Appl. No.: **916,783**

[22] Filed: **Jul. 17, 1992**

Related U.S. Application Data

[63] Continuation of Ser. No. 677,042, Mar. 29, 1991, abandoned.

[51] **Int. Cl.**[5] **A61K 31/445**; C07D 401/12; C07D 211/32

[52] **U.S. Cl.** **514/315**; 514/316; 514/318; 514/320; 514/331; 546/187; 546/190; 546/193; 546/207; 546/208; 546/209; 546/231; 546/233; 546/234; 546/235; 546/238; 546/316; 546/318; 546/320; 546/331

[58] **Field of Search** 546/187, 190, 193, 207, 546/208, 209, 231, 233, 234, 235, 238, 316, 318, 320, 331; 514/315, 316, 318, 320, 331

[56] **References Cited**

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Primary Examiner—C. Warren Ivy
Assistant Examiner—Raymond Covington
Attorney, Agent, or Firm—MaCharri R. Vorndran-Jones; Leroy Whitaker

[57] **ABSTRACT**

3,4,4-trisubstitutedpiperidinyl-N-alkylcarboxylates and intermediates for their preparation are provided. These piperidine-N-alkylcarboxylates are useful as peripheral opioid antagonists.

40 Claims, No Drawings

PERIPHERALLY SELECTIVE PIPERIDINE CARBOXYLATE OPIOID ANTAGONISTS

This application is a continuation of application Ser. No. 07/677,042, filed Mar. 29, 1991 abandoned.

FIELD OF THE INVENTION

This invention relates to 3,4,4-trisubstituted-piperidinyl-N-alkyl-carboxylates and their methods of use as peripheral opioid antagonists.

BACKGROUND OF THE INVENTION

A substantial body of evidence indicates that peripheral opioid peptides and their receptors have a major physiological role in the regulation of gut motility. Consequently gastrointestinal disorders such as idiopathic constipation and irritable bowel syndrome may relate to a dysfunction of opioid receptor mediated control and, agents which act as antagonists for these receptors may benefit a patient suffering from such a dysfunction.

Natural and synthetic opiates such as morphine have been used extensively in the mediation of pain. However, these agents can produce undesirable side effects such as constipation, nausea, and vomiting which are peripheral to the desired action as analgesics. Thus, a peripheral opioid antagonist should not substantially affect the analgesic effects of the opiate while acting to control gastrointestinal function and to minimize the undesirable side effects of the narcotic drug.

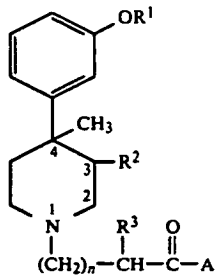
A number of opioid antagonists have been reported including naloxone and naltrexone (Blumberg et al., *Toxicol Appl. Pharmacol.*, 10, 406, 1967). Other derivatives of these compounds have been recently reported (Portoghese et al., *J. Med. Chem.*, 31, 281-282, 1988). 4-Arylpiperidines have also been reported as having analgesic activity and in some instances acting as narcotic antagonists Zimmerman U.S. Pat. No. 4,191,771 (1980); Barnett U.S. Pat. No 4,581,456 (1986); Zimmerman U.S. Pat. No. 4,081,450 (1978) These compounds are disclosed as having useful analgesic activity and in some cases acting as potent narcotic antagonists.

It would be advantageous to have compounds which would act as antagonists to the peripheral effects of opiate analgesics and endogenous opioid peptides. It would also be advantageous if these compounds had a minimal effect on the analgesic activity of the opiate drugs. It would be further advantageous to have compounds which can act to minimize the effects of idiopathic constipation and irritable bowel syndrome.

It has now been found that the N-substituted piperidines of the instant invention are useful as peripherally selective opioid antagonists. The instant compounds can also be useful in relieving the symptoms of idiopathic constipation and irritable bowel syndrome. Certain of the instant compounds are also useful as intermediates in preparing new piperidine compounds.

SUMMARY OF THE INVENTION

The present invention relates to the trans-3,4-isomer of a compound of the Formula



I

wherein:

R^1 is hydrogen or C_1-C_5 alkyl;

R^2 is hydrogen, C_1-C_5 alkyl or C_2-C_6 alkenyl;

R^3 is hydrogen, C_1-C_{10} alkyl, C_3-C_{10} alkenyl, phenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl, or phenyl-substituted C_1-C_3 alkyl;

A is OR^4 or NR^5R^6; wherein:

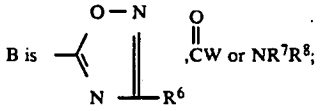
R^4 is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl or phenyl-substituted C_1-C_3 alkyl;

R^5 is hydrogen or C_1-C_3 alkyl;

R^6 is hydrogen, C_1-C_{10} alkyl, C_3-C_{10} alkenyl, cycloalkyl, phenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl, phenyl-substituted C_1-C_3 alkyl, or $(CH_2)_q$-B; or

R^5 and R^6 are each CH_2 which together with N form a 4 to 6 membered heterocyclic ring; wherein

B is



or NR^7R^8; wherein:

R^7 is hydrogen or C_1-C_3 alkyl;

R^8 is hydrogen, C_1-C_{10} alkyl, C_3-C_{10} alkenyl, cycloalkyl-substituted C_1-C_3 alkyl, cycloalkyl, C_5-C_8 cycloalkenyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl, phenyl or phenyl-substituted C_1-C_3 alkyl; or

R^7 and R^8 are each CH_2 which together with N form a 4 to 6 membered heterocyclic ring;

W is OR^9, $NR^{10}R^{11}$, or OE; wherein

R^9 is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl or phenyl-substituted C_1-C_3 alkyl;

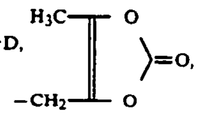
R^{10} is hydrogen or C_1-C_3 alkyl;

R^{11} is hydrogen, C_1-C_{10} alkyl, C_3-C_{10} alkenyl, phenyl, cycloalkyl, C_5-C_8 cycloalkenyl, cycloalkyl-substituted C_1-C_3 alkyl, C_5-C_8 cycloalkenyl-substituted C_1-C_3 alkyl, phenyl-substituted C_1-C_3 alkyl or

or

R^{10} and R^{11} are each CH_2 which together with N form a 4 to 6 membered hetercyclic ring;

E is

E is $(CH_2)_mC(=O)$—D,  or $-R^{12}-OC(=O)R^{13}$

wherein

R^{12} is C_1–C_3 alkyl substituted methylene,

R^{13} is C_1–C_{10} alkyl;

D is OR^{14} or $NR^{15}R^{16}$;

wherein:

R^{14} is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, or phenyl-substituted C_1–C_3 alkyl;

R^{15} is hydrogen, C_{10}–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, phenyl-substituted C_1–C_3 alkyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl or C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl;

R^{16} is hydrogen or C_1–C_3 alkyl; or

R^{15} and R^{16} are each CH_2 which together with N form a 4 to 6 membered heterocyclic ring;

Y is OR^{17} or $NR^{18}R^{19}$;

wherein:

R^{17} is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, or phenyl-substituted C_1–C_3 alkyl;

R^{18} is hydrogen or C_1–C_3 alkyl;

2—CH=CH_2), 1-butanyl (—CH=$CHCH_2CH_3$) and the like.

The term "cycloalkyl" represents C_3–C_8 cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. "Substituted C_5–C_6 cycloalkyl" includes cycloalkyl groups substituted with C_1–C_3 alkyl, C_1–C_3 alkoxyl or halo.

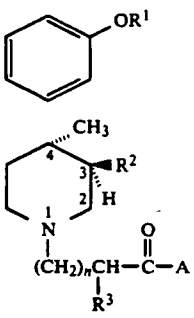
The term "cycloalkyl-substituted C_1–C_3 alkyl" represents a linear C_1–C_3 alkyl group substituted at a terminal carbon with a C_3–C_8 cycloalkyl group. Typical cycloalkyl-substituted alkyl groups include cyclohexylmethyl, cyclohexylethyl, cyclopentylethyl, cyclopentylpropyl and the like.

The term "C_5–C_8 cycloalkenyl" represents and olefinically unsaturated cyclic ring having five to eight carbon atoms.

The term "phenylalkyl" represents a linear C_1–C_3 alkyl chain substituted at a terminal carbon with a substituted or unsubstituted benzene ring. Typical phenylalkyl groups include phenylmethyl, phenylethyl and 3-(4-methylphenyl)propyl.

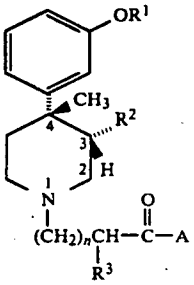
The term "phenyl" includes a benzene ring as well as a benzene ring substituted with one or two C_1–C_2 alkyl groups.

The "4 to 6-membered N-containing heterocyclic ring" referred to herein includes aromatic and nonaromatic rings such as pyrroles and piperidines.



II

or the 3S,4S-isomer of Formula III



III

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" refers to "right" and refers that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" or "left" refers to that configuration of a chiral center with a counterclockwise relationship of group priorties (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (heaviest isotope first). A partial list of priorities and a discussion of stereo chemistry is contained in the book: *The Vocabulary of Organic Chemistry*, Orchin, et al., John Wiley and Sons Inc., publishers, page 126, which is incorporated herein by reference.

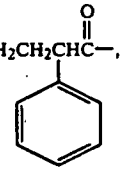
The preferred compounds of the present invention are those of Formula I in which the configuration of substituents on the piperidine ring is 3R and 4R.

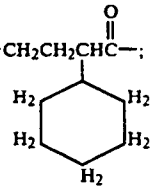
When R^3 is not hydrogen, the carbon atom attached to R^3 is asymmetric. As such, this class of compounds can further exist as the individual R or S stereoisomers at this chiral center, or the racemic mixture of the isomers, and all are contemplated within the scope of the present invention. Preferably, a substantially pure stereoisomer of the compounds of this invention is used, i.e., an isomer in which the configuration at the chiral center is R or S, i.e., those compounds in which the configuration at the three chiral centers is preferably 3R, 4R, S or 3R, 4R, R.

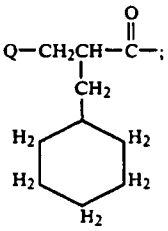
Furthermore, other asymmetric carbons can be introduced into the molecule depending on the structure of A. As such, these classes of compounds can exist as the individual R or S stereoisomers at these chiral centers, or the racemic mixture of the isomers, and all are contemplated as within the scope of the present invention.

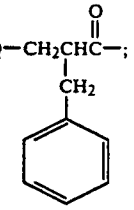
Preferred compounds of the instant invention include the following:

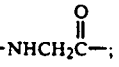
U-OCH_2CH_3; U-OH; G-OH; U-$NHCH_2C(O)NHCH_3$; U-$NHCH_2C(O)NH_2$; G-$NHCH_2C(O)NHCH_3$; U-$NHCH_2C(O)NHCH_2CH_3$; G-$NH(CH_2)_3C(O)OCH_2CH_3$; G-$NHCH_2C(O)OH$; M-$NHCH_2C(O)NH_2$; M-$NH(CH_2)_2C(O)OCH_2(C_6H_5)$; X-$OCH_2CH_3$; X-OH; X-$NH(CH_2)_2CH_3$; Z-$NH(CH_2)_3C(O)OCH_2CH_3$; X-$NHCH_2C(O)OH$; Z-$NH(CH_2)_2N(CH_3)_2$; Z-$NH(CH_2)_2C(O)NHCH_2CH_3$; X-$OCH_2(C_6H_5)$; X-$N(CH_3)_2$; Z-$NH(CH_2)_3C(O)NHCH_3$; Z-$NH(CH_2)_3C(O)NH_2$; Z-$NH(CH_2)_3C(O)NHCH_2CH_3$; X-$OCH_2C(O)OCH_3$; X-$OCH_2C(O)NHCH_3$; and X-$N(CH_3)CH_2C(O)CH_2CH_3$; in which:

U represents  ,

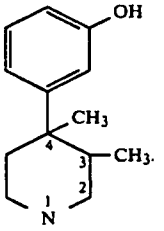
G represents  ;

M represents  ;

Z represents  ;

X represents  ;

wherein:

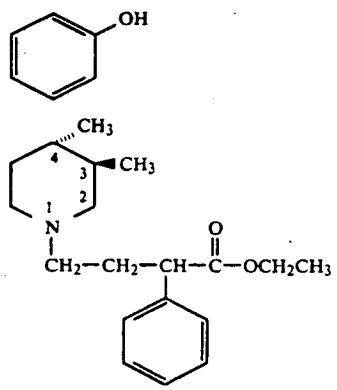
Q represents trans-3,4-dimethyl 

Particularly preferred compounds of the instant invention include the following:

Z-OH; Z-$NH(CH_2)_2C(O)OH$; G-$NH(CH_2)_2C(O)NH_2$; G-$NH(CH_2)_2C(O)NHCH_3$; G-$NHCH_2C(O)NH_2$; G-$NHCH_2C(O)NHCH_2CH_3$; G-$NH(CH_2)_3C(O)NHCH_3$; G-$NH(CH_2)_2C(O)OH$; G-

$NH(CH_2)_3C(O)OH$; X-NH_2; X-$NHCH(CH_3)_2$; X-$OCH_2CH(CH_3)_2$; X-$OCH_2C_6H_5$; X-OH; X-$O(CH_2)_4CH_3$; X-O-(4-methoxycyclohexyl); X-$OCH(CH_3)OC(O)CH_3$; X-$OCH_2C(O)NHCH_2(C_6H_5)$; M-$NHCH_2C(O)OH$; M-$NH(CH_2)_2C(O)OH$; M-$NH(CH_2)_2C(O)NH_2$; U-$NHCH_2C(O)OCH_2CH_3$; and U-$NHCH_2C(O)OH$; wherein Z, G, X and U are as defined above.

The compounds of the instant invention can be named in several ways. For example the compound with the structure IIa



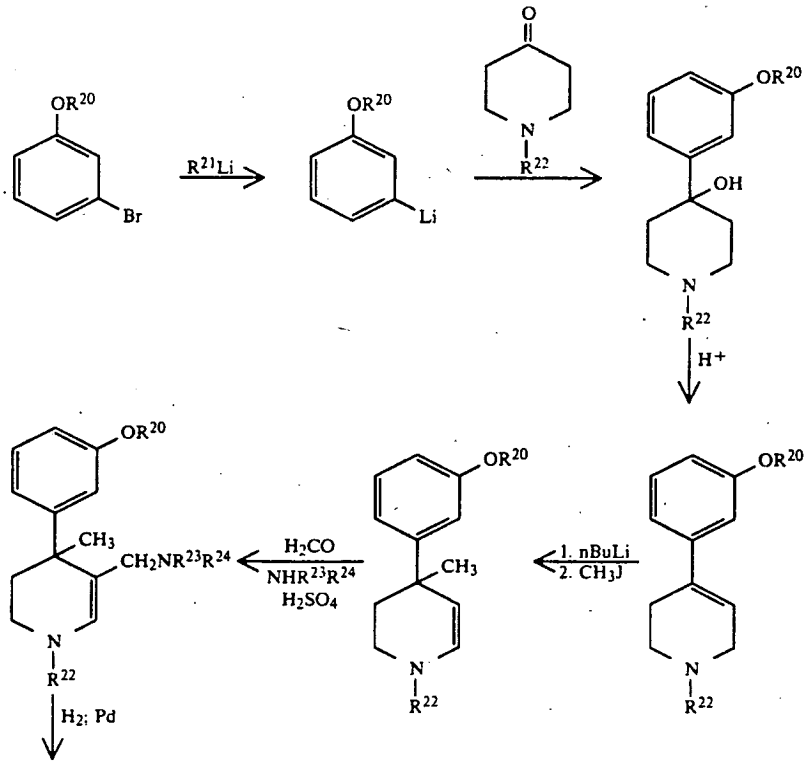
IIa

can be named trans-4-(3-hydroxyphenyl)-3,4-A-phenyl-1-piperidine butanoic acid, ethyl ester or ethyl-trans-4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1piperidinyl]-2-phenylbutanoate.

The piperidines of this invention form pharmaceutically acceptable acid addition salts with a wide variety of inorganic and organic acids. Typical acids used include sulfuric, hydrochloric, hydrobromic, phosphoric, hypophosphoric, hydroiodic, sulfamic, citric, acetic, maleic, malic, succinic, tartaric, cinnamic, benzoic, ascorbic, mandelic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, trifluoroacetic, hippuric and the like.

The compounds of the present invention can be prepared by a variety of procedures well known to those of ordinary skill in the art. The 3-substituted-4-methyl-4-(3-hydroxy- or alkanoyloxyphenyl)piperidine derivatives employed as starting materials in the synthesis of the instant compounds can be prepared by the general procedure taught by Zimmerman in U.S. Pat. No. 4,115,400 (1978), and Zimmerman et al. in U.S. Pat. No. 4,891,379 (1990) both incorporated herein by reference The starting material for the synthesis of the compounds of the present invention, (3R,4R)-4-(3-hydroxypheny)-3,4-dimethylpiperidine, can be prepared by the procedure of Barnett in U.S. Pat. 4,581,456, herein incorporated by reference, but adjusted as described in such patent so that the β-stereochemistry is preferred. This process is depicted in Scheme 1, wherein R^{20} is C_1–C_3 alkyl, R^{21} is C_1–C_6 alkyl, R^{22} is C_1–C_4 alkyl; R^{23} and R^{24} independently are C_1–C_3 alkyl or, when taken together with the nitrogen atom to which they are attached, form piperidine, piperazine, N-methylpiperazine, morpholine or pyrrolidine, and J is halogen, preferably chlorine or bromine.

Scheme 1



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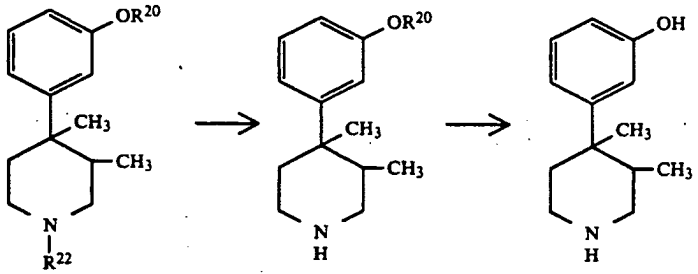
Scheme 1



The first step of the above-described process involves the formation of the 3-alkoxyphenyllithium reagent by reacting 3-alkoxybromobenzene with an alkyl-lithium reagent. This reaction is typically performed under inert conditions and in the presence of a suitable non-reactive solvent such as dry diethyl ether or preferably dry tetrahydrofuran. Preferred alkyllithium reagents used in this process are n-butyllithium, and especially sec.-butyllithium. Generally, approximately an equimolar to slight excess of alkyllithium reagent is added to the reaction mixture. The reaction is conducted at a temperature between about −20° C. and about −100° C., more preferably from about −50° C. to about −55° C.

Once the 3-alkoxyphenyllithium reagent has formed, approximately an equimolar quantity of a 1-alkyl-4-piperidone is added to the mixture while maintaining the temperature between −20° C. and −100° C. The reaction is typically complete after about 1 to 24 hours. At this point, the reaction mixture is allowed to gradually warm to room temperature. The product is isolated by the addition to the reaction mixture of a saturated sodium chloride solution in order to quench any residual lithium reagent. The organic layer is separated and further purified if desired to provide the appropriate 1-alkyl-4-(3-alkoxyphenyl)piperidinol derivative.

The dehydration of the 4-phenylpiperidinol prepared above is accomplished with a strong acid according to well known procedures. While dehydration occurs in various amounts with any one of several strong acids such as hydrochloric acid, hydrobromic acid, and the like, dehydration is preferably conducted with phosphoric acid, or especially p-toluenesulfonic acid in toluene or benzene This reaction is typically conducted under reflux conditions, more generally from about 50° C. to about 150° C. The product thus formed is generally isolated by basifying an acidic aqueous solution of the salt form of the product and extracting the aqueous solution with a suitable water immiscible solvents. The resulting residue following evaporation can then be further purified if desired.

The 1-alkyl-4-methyl-4-(3-alkoxyphenyl)tetrahydropyridine derivatives are prepared by a metalloenamine alkylation. This reaction is preferably conducted with n-butyllithium in tetrahydrofuran (THF) under an inert atmosphere, such as nitrogen or argon. Generally, a slight excess of n-butyllithium is added to a stirring solution of the 1-alkyl-4-(3-alkoxyphenyl)-tetrahydropyridine in THF cooled to a temperature in the range of from about −50° C. to about 0° C., more preferably from about −20° C. to about −10° C. This mixture is stirred for approximately 10 to 30 minutes followed by the addition of approximately from 1.0 to 1.5 equivalents of methyl halide to the solution while maintaining the temperature of the reaction mixture below 0° C. After about 5 to 60 minutes, water is added to the reaction mixture and the organic phase is collected. The product can be purified according to standard procedures, but the crude product is preferably purified by either distilling it under vacuum or slurrying it in a mixture of hexane:ethyl acetate (65:35, v:v) and silica gel for about two hours. According to the latter procedure, the product is then isolated by filtration followed by evaporating the filtrate under reduced pressure.

The next step in the process involves the application of the Mannich reaction of aminomethylation to non-conjugated, endocyclic enamines. This reaction is preferably carried out by combining from about 1.2 to 2.0 equivalents of aqueous formaldehyde and about 1.3 to 2.0 equivalents of a secondary amine $NHR^{23}R^{24}$ in a suitable solvent. While water is the preferred solvent, other non-nucleophilic solvents such as acetone and acetonitrile can also be employed in this reaction. The pH of this solution is adjusted to approximately 3.0–4.0 with an acid which provides a non-nucleophilic anion. Examples of such acids include sulfuric acid, the sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acid, phosphoric acid, and tetrafluoroboric acid. The preferred acid is sulfuric acid. To this solution is added one equivalent of a 1-alkyl-4-methyl-4-(3-alkoxyphenyl)tetrahydropyridine, typically dissolved in aqueous sulfuric acid, and the pH of the solution is readjusted with the non-nucleophilic acid or a secondary amine as defined above. The pH should be maintained in the range of from about 1 0 to 5.0 with a pH of about 3 0 to 3.5 being preferred during the reaction. The reaction is substantially complete after about 1 to 4 hours, more typically about 2 hours, when conducted at a temperature in the range of from about 50° C. to about 80° C., more preferably at about 70° C. The reaction is next cooled to approximately 30° C. and added to a sodium hydroxide solution. This solution is extracted with a water immiscible organic solvent, such as hexane or ethyl acetate, and the organic phase, following thorough washing with water to remove any residual formaldehyde, is evaporated to dryness under reduced pressure.

The next step of the process involves the catalytic hydrogenation of the 1-alkyl-4-methyl-4-(3-alkoxyphenyl)-3-tetrahydropyridinemethanamine prepared above to the corresponding trans-1-alkyl-3,4-dimethyl-4-(3-alkoxyphenyl)piperidine. This reaction actually occurs in two steps. The first step is the hydrogenolysis reaction wherein the exo C-N bond is reductively cleaved to generate the 3-methyltetrahydropyridine. In the second step, the 2,3-double bond in the tetrahydropyridine ring is reduced to afford the desired piperidine ring.

Reduction of the enamine double bond introduced the crucial relative stereochemistry at the 3 and 4 carbon atoms of the piperidine ring. The reduction does not occur with complete stereoselectivity. The catalysts employed in the process are chosen from among the various palladium and preferably platinum catalysts.

The catalytic hydrogenation step of the process is preferably conducted in an acidic reaction medium. Suitable solvents for use in the process include the alcohols, such as methanol or ethanol, as well as ethyl acetate, tetrahydrofuran, toluene, hexane, and the like.

Proper stereochemical outcome has been found to be dependent on the quantity of catalyst employed. The quantity of catalyst required to produce the desired stereochemical result is dependent upon the purity of the starting materials in regard to the presence or absence of various catalyst poisons.

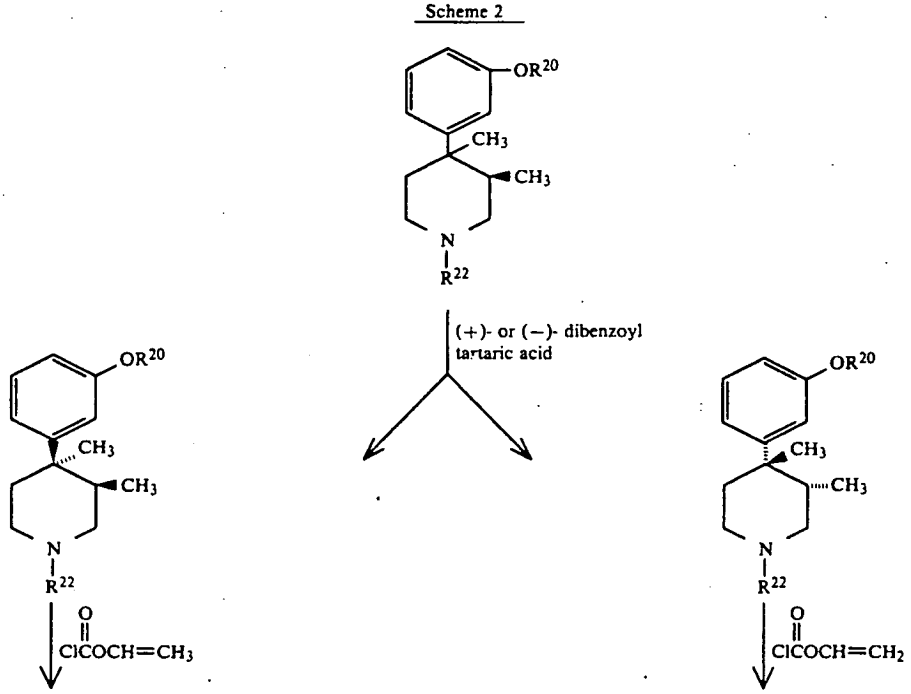
The hydrogen pressure in the reaction vessel is not critical but can be in the range of from about 5 to 200 psi. Concentration of the starting material by volume is preferably around 20 ml. of liquid per gram of starting material, although an increased or decreased concentration of the starting material can also be employed. Under the conditions specified herein, the length of time for the catalytic hydrogenation is not critical because of the inability for over-reduction of the molecule. While the reaction can continue for up to 24 hours or longer, it is not necessary to continue the reduction conditions after the uptake of the theoretical two moles of hydrogen. The product is isolated by filtering the reaction mixture for example through infusorial earth, and evaporating the filtrate to dryness under reduced pressure. Further purification of the product thus isolated is not necessary and preferably the diastereomeric mixture is carried directly on to the following reaction.

The alkyl substituent is next removed from the 1-position of the piperidine ring by standard dealkylation procedures. Preferably, a chloroformate derivative, especially the vinyl or phenyl derivatives, are employed and removed with acid. Next, the alkoxy compound prepared above is dealkylated to the corresponding phenol. This reaction is generally carried out by reacting the compound in a 48% aqueous hydrobromic acid solution. This reaction is substantially complete after about 30 minutes to 24 hours when conducted at a temperature between 50° C. to about 150° C., more preferably at the reflux temperature of the reaction mixture. The mixture is then worked up by cooling the solution, followed by neutralization with base to an approximate pH of 8. This aqueous solution is extracted with a water immiscible organic solvent. The residue following evaporation of the organic phase is then preferably used directly in the following step.

The compounds employed as starting materials to the compounds of the invention can also be prepared by brominating the 1-alkyl-4-methyl-4-(3-alkoxyphenyl)-3-tetrahydropyridinemethanamine prepared above at the 3-position, lithiating the bromo compound thus prepared, and reacting the lithiated intermediate with a methylhalide such as methyl bromide to provide the corresponding 1-alkyl-3,4-dimethyl-4-(3-alkoxyphenyl)tetrahydropyridinemethanamine. This compound is then reduced and converted to the starting material as indicated above.

As noted above, the compounds of the present invention can exist as the individual stereoisomers. Preferably reaction conditions are adjusted as disclosed by Barnett (supra) or as set forth in Example 1 hereof to be substantially stereoselective and provide a racemic mixture of essentially two enantiomers. These enantiomers can then be resolved. The preferred procedure employed to prepare the resolved starting materials used in the synthesis of these compounds includes treating a racemic mixture of alkyl-3,4-dimethyl-4-(3-alkoxyphenyl)piperidine with either (+)- or (−)-di-benzoyl tartaric acid to provide the resolved intermediate. This compound is dealkylated at the 1-position with vinyl chloroformate and finally converted to the desired 4-(3-hydroxyphenyl)piperidine isomer. This reaction scheme is represented in the following Scheme 2:

Scheme 2



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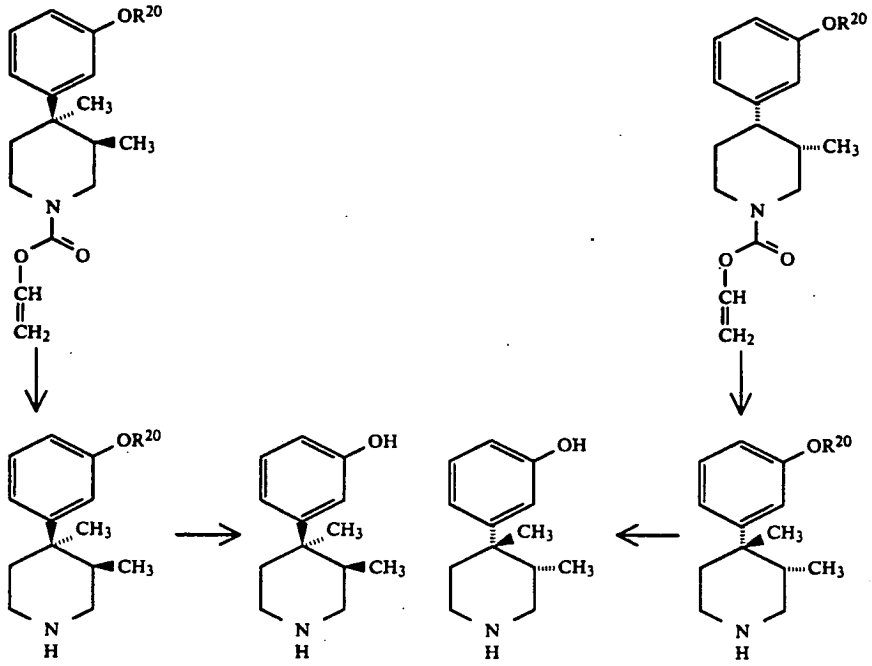
Scheme 2



wherein R^{20} and R^{22} are as defined above.

As will be understood by those skilled in the art, the individual enantiomers of the invention can also be isolated with either (+) or (−) dibenzoyl tartaric acid, as desired, from the corresponding racemic mixture of the compounds of the invention. Preferably the (+)-trans enantiomer is obtained.

Although the (+)trans-3,4 stereoisomer is preferred, all of the possible stereoiosmers of the instant compounds are within the contemplated scope of the present invention. Racemic mixtures of the stereoisomers as well as the substantially pure stereoisomers are within the scope of the invention. The term "substantially pure" is used herein to refer to at least about 90 mole percent, more preferably at least about 95 mole percent and most preferably at least about 98 mole percent of the desired stereoisomer is present compound to other possible stereoisomers.

Intermediates and compounds with the instant invention can be prepared by reacting a 3,4-alkyl-substituted-4-(3-hydroxyphenyl)piperidine with a compound of the formula $LCH_2(CH_2)_{n-1}CHR^3C(O)E$ where L is a leaving group such as chlorine, bromine or iodine, E is a carboxylic acid, ester or amide, and R^8 and n are as defined hereinabove. Preferably L is chlorine and the reaction is carried out in the presence of a base to alkylate the piperidine nitrogen. For example 4-chloro-2-cyclohexylbutanoic acid, ethyl ester can be contacted with (3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidine to provide 4-[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidine]butanoic acid, ethyl ester. Although the ester of the carboxylic acid is preferred, the free acid itself or an amide of the carboxylic acid can be used.

In alternative synthesis, the substituted piperidine can be contacted with an e-methylene alkyl ester to alkylate the piperidine nitrogen. For example, 2-methylene-3-phenylproponic acid, ethyl ester can be contacted with a desired piperidine to provide 2-benzyl-3-piperidine-propanoic acid ethyl ester.

Another synthetic route can involve the reaction of a substituted piperidine with a haloalkylnitrile. The nitrile group of the resulting piperidine alkylnitrile can be hydrolyzed to the corresponding carboxylic acid.

With each of the synthetic routes, the resulting ester or carboxylic acid can be reacted with an amine or alcohol to provide modified chemical structures. In the preparation of amides, the piperidine-carboxylic acid or -carboxylic acid ester is reacted with an amine in the presence of a coupling agent such as dicyclohexylcarbodiimide, boric acid, borane-trimethylamine, and the like. Esters can be prepared by contacting the piperidine-carboxylic acid with the appropriate alcohol in the presence of a coupling agent such as p-toluenesulfonic acid, boron trifluoride etherate or N,N'-carbonyldiimidazole. Alternatively, the piperidine-carboxylic acid chloride can be prepared using a reagent such as thionyl chloride, phosphorus trichloride, phosphorus pentachloride and the like. This acyl chloride can be reacted with the appropiate amine or alcohol to provide the corresponding amide or ester. Examples of such reactions are provided in the appended examples.

The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the claimed invention.

As used in the instant examples, the following terms have the meanings indicated. "Hobt" refers to 1-hydroxybenzotriazole hydrate "THF" refers to tetrahydrofuran. "DMF" refers to dimethylformamide. "TEA" refers to triethylamine. "DCC" refers to dicyclohexylcarbodiimide.

The column chromatography procedure used involved gravitational flow with Allied Fischer silica gel (70–150 mesh). Gradient solvent procedures were employed using the solvent systems specified in the particular example. The gradient procedure involved starting the indicated solvent system and incrementally chang-

ing the solvent mixture until the indicated final solvent system was obtained. Fractions containing product were evaporated generally under reduced vacuum to provide product.

Preparative liquid chromatography was performed with the Waters Prep LC/500 apparatus using dual silica prep pack cartridges. Gradient solvent systems were employed as listed in the particular example.

Optical rotations were determined using methanol as the solvent.

For those examples indicated, purification of the specified compound was accomplished by preparative, centrifugal, thin layer chromatography on a Harrison Model 7924A Chromatron using Analtech silica gel GF rotors. The plate thickness and solvent system employed are indicated in the particular example.

The hydrochloride salt of the particular compound was prepared by placing the free base into ethyl ether. While stirring this ether solution, a solution of HCl in ethyl ether was added dropwise until the base-containing solution became acidic. A preciptate formed which was filtered and dried to provide the corresponding hydrochloride salt of the free base.

In the instant Examples Q-, X-, Z-, M-, G-, and U- are used to represent the moieties indicated hereinabove.

EXAMPLE 1

Preparation of (+)-(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidine [Q-H]

3-Bromophenol was combined with an equal molar amount of 2-bromopropane in ethanol and in the presence of potassium carbonate to provide 3-bromoisopropoxybenzene.

The 3-bromo-i-propoxybenzene (200 g, 0.08703 mol) was combined with THF (540 ml) under nitrogen and cooled to about −75° C. n-Butyl lithium (565 ml, 0.8306 mol) was added dropwise while maintaining the mixture at less than −70° C. After 2 hours 1,3-Dimethyl-4-piperidone (106.7 g, 0.8389 mol) was added while maintaining the temperature of the mixture between −80° C. and −70° C. After stirring 2 hours at −70° C., the reaction mixture was then added to 6N HCl (280 ml) while maintaining the temperature at 20°-25° C. The pH was adjusted to 1 with 12-N HCl. The aqueous layer containing product was separated and heptane (320 ml) was added along with 50% NaOH (48 ml, pH=13-14) and the resulting mixture allowed to stand overnight. The mixture was heated to 45°-50° C. and the upper layer was separated. The remaining aqueous layer was extracted with heptane (320 ml) at 45°-50° C. The combined organic fractions were washed with de-ionized water (120 ml) at 45°-50° C. The resulting organic layer was vacuum distilled at a pot temperature of about 55° C. at 100 mmHg. Crystallization from heptane and drying provided 151.8 g of 3-(3-i-propoxyphenyl)-1,3-dimethyl-4-hydroxypiperidine. Melting point 75.0°-76.0° C.

This 4-hydroxypiperidine (463 g, 1.758 mol) was combined with ethyl acetate (2275 ml) under nitrogen. The solution was cooled to 0°-5° C. and ethyl chloroformate (205 ml, 2.144 mol) was added while maintaining the temperature below 15° C. The reaction mixture was stirred for an additional 3 hours at room temperature. The mixture was then added to 5N NaOH (750 ml) with stirring (pH=12-13) the organic layer was separated and washed with de-ionized water. Solvent was removed by evaporation at 50° C. to provide 591 g of a viscous oil.

This viscous oil (284.8 g) was dissolved in ethanol (2.6 L) and warmed to 55° C. under nitrogen. (+)-Di-p-toluoyl-D-tartaric acid, monohydrate was added and the solution heated to reflux. After stirring overnight at room temperature, the mixture was cooled to 0°-5° C. before filtering. The filter cake was washed with cold ethanol, air dried for 30 minutes then vacuum dried at 45°-50° C. Recrystallization from ethanol provided 201.7 g of product with a melting point of 153.5°-155° C. (dec). This material had a ratio of isomers by proton NMR of 97:3.

Product prepared in this manner (411.7 g) was added to heptane (1200 ml) and 2N NaOH (550 ml) over a 15 minute period. pH of the mixture was adjusted to about 13 with 50% NaOH and stirred until all solid had dissolved. The layers were separated and the organic layer washed with 1N NaOH (275 ml), de-ionized water (275 ml) and the saturaed aqueous sodium chloride (210 ml). The organic fraction was dried over 175 g of sodium sulfate, filtered and washed with heptane (125 ml). The solvent was removed by evaporation to provide 189.4 g of a colorless viscous oil. $[\alpha]_{589}$ of −6.92° (c=1.01, methanol).

This viscous oil product (50.0 9) and decalin (250 ml) were heated at 190°-195° C. for 19 hr under nitrogen while removing the ethanol formed by distillation. The solution was cooled to 15°-20° C. under nitrogen and 1N HCl (155 ml) was added with stirring. The aqueous fraction was separated and extracted with heptane (2×30 ml). The pH of the aqueous layer was adjusted to about 13 by adding 50% NaOH and extracted with heptane 36.5 g of a yellow-orange liquid were removed from the organic layer. $[\alpha]_{589}=-67.24°$.

This yellow-orange liquid product (19.6 g) was combined with THF (175 ml) and cooled to −15° C. to −20° C. under nitrogen. n-Butyl lithium (70.0 ml) was added with stirring over about 0.5 hr while maintaining the internal temperature at about −10° C. to about −20° C. The mixture was stirred for another 0.5 hr at −10° C. to −15° C. and then cooled to −45° to −50° C. Dimethyl sulfate (7.7 ml) was added slowly over 20-30 minutes while maintaing the temperature between −45° C. and −50° C. The mixture was then stirred for an additional 30 minutes at about −50° C. This reaction mixture was then added slowly to a dilute solution of aqueous ammonium hydroxide (15.5 ml aqueous ammonium hydroxide solution plus 55 ml de-ionized water) at 0°-5° C. The mixture was warmed to 20°-25° C. over 30-45 minutes and stirred an additional 2 hrs at 20-25° C. The organic layer was recovered and washed with de-ionized water followed by removal of solvent by evaporation to provide 21.44 g of 4-(3-i-propoxyphenyl)-1,4,5-trimethyl-2,3-dehydropiperidine as an orange liquid.

This dehydropiperidine (21.2 g) and methanol (195 ml) were combined under nitrogen and cooled to 0°-5° C. Sodium borohydride (4.2 g) was added slowly while maintaining the temperature below 15° C. The reaction mixture was stirred at room temperature for 3 hrs. Acetone (21 ml) was added to the reaction mixture and stirred for 5 minutes. A saturated solution of sodium bicarbonate (25 ml) was added and the mixture stirred for 5 minutes. The alcohols were removed by evaporation at 50° C. De-ionized water (95 ml) and ethyl acetate (95 ml) were added and the resulting mixture stirred to form a solution. Phases were separated and the aqueous

phase extracted with ethyl acetate (20 ml). Combined organic fractions were washed with de-ionized water (95 ml) and the solvent removed by evaporation at 50° C. to provide (+)-4-(3-i-propoxyphenyl)-1,3,4-trimethylpiperidine as a yellow liquid (20.5 g).

Anhydrous ethanol (75 ml) and (+)-di-p-toluoyl-D-tartaric acid, monohydrate (12.48 g) were combined and heated to 55°–60° C. under nitrogen. An ethanol solution of the trimethyl piperidine (8.07 g in 20 ml) was added while heating to reflux (about 75° C.). De-ionized water (6 ml) was added to obtain a clear homogeneous solution which was stirred at reflux for 0.5 hr. Cooling, filtering, washing with cold ethanol, and drying provided 15.07 g of (+)-4-(3-i-propoxyphenyl)-1,3,4-trimethylpiperidine·(+)-di-p-toluoyl-D-tartaric acid salt with a melting point 145°–147.5° C. (dec).

Toluene (1400 ml) and 2N NaOH (700 ml) were combined and cooled to 15°–20° C. The piperidine-tartaric salt (395.0 grams) was added with stirring at 15°–25° C. and stirring continued until all solids had dissolved. The layers were separated and the organic fraction washed with 1N NaOH (385 ml) and di-ionized water (385 ml). The organic fraction was filtered and the solvent removed by evaporation (50° C.) to provide 164.8 g of the free base as an oil. $[\alpha]_{589} = +74.18°$.

To a mixture of the free base (+)-4-(3-i-propoxyphenyl)-1,3,%-trimethyl-piperidine (25 g) in toluene (160 ml) at 80–90° C. was added phenylchloroformate (17.2 g). The mixture was heated at reflux (110° C.) for 2 hrs and then cooled to 45°–50° C. NaOH (5 ml, 50%, in 40 ml water) was added and the mixture stirred with cooling to room temperature. After 30 minutes the layers were separated and the organic layer washed with a 1:1 mixture of methanol and 1N HCl, a 1:1 mixture of methanol and 1N NaOH, and then washed with water. Evaportion of the solvent provided 33.9 g of the phenyl carbamate as an oil.

The phenyl carbamate (13.95 g), 48% HBr (17.4 ml) and glacial acetic acid (4.7 ml) were combined and refluxed for 18 hours. The solution was cooled to room temperature; water (50 ml) was added; and the solution was extracted 3 times with t-butyl methyl ether (30 ml aliquots). The pH of the aqueous phase was adjusted to 8.5–8.8 with 50% NaOH solution. Methanol (15 ml) was added and the pH adjusted to 10.5 with the 50% NaOH solution. The mixture was stirred for 1.5 hours, cooled to 5° C. and filtered to provide the white solid (+)-trans-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (6.86 g). $[\alpha]_{589} = +380.37$ (methanol).

EXAMPLE 2

Preparation of 3-phenyl-2-(ethoxycarbonyl)-1-propene

N-butyl lithium (201 ml of 1.6M) was added dropwise to diisopropyl amine (45 ml) in dry tetrahydrofuran (870 ml) at −78° C. After stirring at this temperature for 0.5 hours ethyl-2-benzylacetoacetate (39.6 g, 0.18M) in THF (250 ml) was added dropwise at 0° C. After stirring for 20 minutes, paraformaldehyde (35.42 g) was added at room temperature followed by stirring for one hour and refluxing for 4 hours. The reaction mixture was filtered and the liquid evaporated to dryness. The residue was dissolved in a mixture of $KHCO_3/H_2O$ and methylene chloride (1:1) and stirred for 0.5 hours. The layers were separated and the methylene chloride layer was dried over K_2CO_3 and then evaporated to dryness to yield 46.4 g of named product. This product was purified with a Prep-500 chromatograph eluting with hexane to 5% ethyl acetate/hexane gradient to yield 30 g of a clear liquid. ms (fd) = 190M+

EXAMPLE 3

Preparation of 3-cyclohexyl-2-(ethoxycarbonyl)-1-propene

A. Ethyl-2-benzylacetoacetate (50 g, 0.227M) was dissolved in ethanol (435 ml) and combined with 5% Rh/Al_2O_3 (15 g) and stirred at room temperature overnight under hydrogen pressure (60 psi). The mixture was filtered and solvent removed under vacuum. The residue was diluted with ethyl acetate and washed with water. The organic layer was dried over K_2CO_3 and the solvent removed under vacuum to provide 49 g of ethyl-2-aceto-3-cyclohexylpropanoate.

B. Ethyl-2-acetohexylpropanoate (20 g) was contacted with N-butyllithium (101 mL 1.6M), diisopropylamine (23 mL in dry THF, 440 mL) and paraformaldehyde (18 g) as in Example 2 to provide 19 g of crude product which was purified by bulb-to-bulb distillation at 130° C., 0.1 mmHg to provide 10 g of the named product as a clear liquid.

ms (fd) = 196M+

EXAMPLE 4

A. Preparation of trans-4-(3-hydroxyphenyl)-3,4-dimethyl-a-(phenylmethyl)-1-piperidinepropanoic acid, ethyl ester hydrochloride [Z-OCH_2CH_3·HCl]

Trans-(+)-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (6.0 g, 29 mmole) and 3-phenyl-2-(ethoxycarbonyl)-1-propene (6.1 g) were dissolved in methanol (300 ml) and stirred at room temperature under nitrogen. During the 10 day reaction time, the mixture was evaporated two times and rediluted with methanol on days 5 and 9. On day 10 the mixture was evaporated to dryness to provide 13 g of solid which was passed through a silica column eluting with hexane to ethyl acetate gradient providing 11.4 g of purified product. Analysis for $C_{25}H_{33}NO_3$·HCl: Theory: C, 69.50; H, 7.93; N, 3.24, Found: C, 69.36; H, 7.69; N, 3.21.

B. Preparation of 4-(3-hydroxyphenyl)-3,4-dimethyl-a-(phenylmethyl)-1-piperidinepropanoic acid monohydrate [Z-OH·H_2O]

To 1.0 g of the product from 4A was added dioxane (60 ml) and 6 N HCl (30 ml). The mixture was heated to reflux for two hours, cooled and the solvent removed under vacuum. The residue was rediluted with water and the pH adjusted to 9.8 with ammonium hydroxide. The desired acid was extracted with 3:1 butanol/toluene solution. The solvent was removed and the residue was passed through a silica column eluting with a mixture of methanol and ethyl acetate (20:80, v:v). The resulting material was slurried in ethyl ether, and filtered to give 650 mg of product having m.p. 120°–131° C.

Analysis for $C_{23}H_{31}NO_4$: Theory: C, 71.66, H, 8.11; N, 3.63; Found : C, 71.89; H, 8.09; N, 3.71.

EXAMPLE 5

A. Preparation of 3-(3,4-dimethyl-4-(3-hydroxyphenyl)-1-piperidinyl]-2-(cyclohexylmethyl)propanoic acid ethyl ester hydrochloride

[M-OCH_2CH_3·HCl]

The procedure of Example 4A was used with trans-(±)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (4.0 g)

and 2-(ethoxycarbonyl)-3-phenyl-1-propene (4.61 g). The solvent was removed under vacuum and the residue diluted with ethyl acetate and water. The pH was adjusted to 9.8 with IN NaOH and the mixture was extracted with ethyl acetate. This organic layer was dried over K_2CO_3. The solvent removed to yield 4.3 g. The HCl-salt was prepared having a melting point 101°-111° C.

Analysis for $C_{25}H_{39}NO_3$·HCl: Theory: C, 68.55; H, 9.20; N, 3.19; Found : C, 68.32; H, 9.16; N, 3.18.

B. Preparation of 3-[3,4-dimethyl-4-(3-hydroxyphenyl)-1-piperidinyl]-2-(cyclohexylmethyl)-propanoic acid monohydrate [M-OH·H_2O]

2.88 g of compound from preparation 5A was added to dioxane (75 ml) and 6N HCl (75 ml) and allowed to reflux with stirring for five hours. The solvent was removed under reduced pressure and the residue was taken into H_2O. The pH of the water was adjusted to 9.8 with ammonium hydroxide. The solution was extracted with a mixture of butanol and toluene (3:1, v:v) and dried over magnesium sulfate. The solvent was removed by vacuum to yield 2.6 g of solid. This material was purified by column chromatography eluting with a 1:1 ethyl acetate-methanol mixture. After removal of solvent, the material was triturated with ethyl ether and filtered to give 640 mg of product. m.p. = 145°-150° C.

Analysis for $C_{23}H_{35}NO_3$·H_2O: Theory: C, 70.55; H, 9.52; N, 3.57; Found : C, 70.78; H, 9.34; N, 3.54.

EXAMPLE 6

Preparation of ethyl-2-phenyl-4-chlorobutanoate

Diisopropylamine (2.71 ml, 1.1 eq) was added to dry THF (10 ml) and cooled to −78° C. N-butyllithium (11.01 ml of 1.6 Molar, 1.1 eq) was added dropwise. The mixture was stirred at -78° C. for 30 minutes and ethyl-2-phenylacetate (2.9 g, 1.0 eq) was dissolved in dry THF (20 ml) and the solution added dropwise to the reaction mixture. The mixture was stirred at −78° C. for 0.25 hour and then allowed to warm to −30° C. and stirred for an additional 0.25 hour. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (2.13 ml, 1.0 eq) was dissolved in dry THF (20 ml) and added dropwise to the mixture. The resulting mixture was maintained at −30° C. for ten minutes. This mixture was then cannulated under N_2 pressure to a flask which had been charged with ethyl ether (100 ml) and 1-bromo-2-chloroethane (7.3 ml, 5.0 eq) at −10° C. The mixture was stirred for three hours at −10° C. to −5° C. The mixture was cooled to −30° C. and quenched with a saturated ammonium chloride solution. The mixture was extracted with ethyl ether which was then dried over K_2CO_3. The solvent was stripped to provide 3.2 g of product which distilled at 70°-71° C. under 0.01 mmHg.

ms (fd) = 226M+

EXAMPLE 7

Preparation of ethyl-2-cyclohexyl-4-chlorobutanoate

Diisopropylamine (2.71 ml, 1.1 eq.) was added to dry THF (10 ml) and cooled to -78° C. N-Butyllithium (11.01 ml of 1.6 Molar solution, 1.0 eq.) was added and the mixture stirred at -78° C. for 0.5 hour. To this mixture was then added dropwise a solution of ethyl-2-cyclohexylacetate (3.0 g, 1.0 eq.) in THF (20 ml) at −78° C. and stirred for 0.5 hour. DMPU (2.13 ml, 1.0 eq.) in THF (20 ml) was added dropwise and allowed to stir at −78° C. for 10 minutes. To this mixture was added 1-bromo-2-chloroethane (1.46 ml, 1.0 eq.) in THF (10 ml) and the mixture stirred at −5° C. for 15 minutes. The mixture was then warmed to room temperature and stirred for 1.0 hour. The mixture was cooled to 0° C., quenched with saturated ammonium chloride solution, extracted with ethyl ether and the ether layer was washed three times with water. The organic layer was separated, dried over K_2CO_3 and the solvent removed to provide 3.6 g of product. This was fractionally distilled to provide 3.0 g of product Boiling Point 66°-70° C. at 0.05 mmHg.

Analysis for $C_{12}H_{21}O_2Cl$; Theory: C, 61.93; H, 9.09; Found: C, 61.66; H, 9.23.

EXAMPLE 8

A. Preparation of trans-4-[(3-Hydroxyphenyl)-3,4-dimethyl-1-piperidine]-2-phenyl butanoic acid, ethyl ester hydrochloride [U-OCH_2CH_3·HCl]

Ethyl-4-chloro-2-phenylbutanoate (2.43 g), trans-(+)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine [Q-OH] (2.0 g), $NaHCO_3$ (905 mg), NaI (1.53 g), and dimethylformamide (DMF) (120 ml) were combined and heated to reflux for two hours. The mixture was cooled and evaporated to dryness. The solid was taken into H_2O and the pH adjusted to 9.8 with 1N NaOH. This mixture was extracted with ethyl acetate and the organic layer dried over K_2CO_3. The solvent was removed under vaccum to provide 5 g of crude product. This product was subjected to column chromatography eluting with ethyl acetate to provide 4.0 g of material. This material was converted to the HCl salt.

Analysis: $C_{25}H_{33}N_3O$·HCl Theory: C, 69.51; H, 7.93; N, 3.24; Found: C, 69.72; H, 7.77; N, 3.34.

EXAMPLE 8B

B. Preparation of trans-4-[(3-Hydroxyphenyl)-3,4-dimethyl-1-piperidine]-2-phenyl butanoic acid hydrochloride [U-OH·HCl]

The ethyl ester product of Example 8A (3.0 g) was combined with 6N HCl (250 ml) and dioxane (30 ml). The mixture was stirred at reflux for 18 hours. The solvent was removed under vacuum. The residue was taken into H_2O, the pH was adjusted to 9.8 with TEA and the desired product extracted with a 3:1 butanol-toluene solution. The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum to yield 2.6 g white solid. The compound was converted to the HCl salt. m.p. = 140°-150° C.

Analysis: $C_{23}H_{29}N_3O$·HCl Theory: C, 68.39; H, 7.49; N, 3.47; Found: C, 68.19; H, 7.27; N, 3.47.

EXAMPLE 9

A. Preparation of trans-4-[(3-hydroxyphenyl)-3,4-dimethyl-1-piperidine]-2-cyclohexylbutanoic acid, ethyl ester hydrochloride [G-OCH_2CH_3·HCl]

DMF (80 ml) was added to trans-(+)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (1.0 g) followed by NaI (735 mgs, 1.0 eq), K_2CO_3 (677 mgs, 1.0 eq) and then ethyl 4-chloro-2-cyclohexylbutanoate (1.0 eq). The mixture was refluxed for 2 hours, cooled and poured into water. The pH was adjusted to 9.8 with 1 NaOH. The mixture was extracted with ethyl ether and the organic layer dried over K_2CO_3. The solvent was removed under vacuum to provide 1.6 g of solid. The hydrochloride salt was prepared to yield 1.1 g of a white solid.

m.p. 80°-95° C.

Analysis: $C_{25}H_{39}NO_3$·HCl Theory C, 68.55; H, 9.20; N, 3.20; Found: C, 68.27; H, 9.18; N, 3.37.

EXAMPLE 9B

Preparation of trans-4-[(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-cyclohexylbutanoic acid hydrochloride [G-OH·HCl]

Product (HCl salt) from Example 9A (1.0 g) was combined with 6N HCl (100 ml) and the mixture refluxed for 18 hours. The hot mixture was filtered and the filtrate evaporated under vacuum to provide a white solid. The solid was triturated with ethyl acetate and filtered. The white solid was dried in a vacuum oven to provide 600 mg as the HCl salt. This salt was taken into water and the pH adjusted to 9.8 with TEA. The product was extracted with a 3:1 butanol:toluene mixture and dried over $MgSO_4$. The solvent was removed to provide 460 mg of product as a white solid. The HCl salt was made.

m.p. = 140°-160° C. (foam)

Analysis: $C_{23}H_{35}NO_3$·HCl: Theory: C, 67.38; H, 8.85; N, 3.42; Found: C, 67.44; H, 8.94; N, 3.58.

EXAMPLE 10

Preparation of trans-4-[(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-phenyl-N,N-dimethylbutanamide hydrochloride [U-N$(CH_3)_2$·HCl]

Acid prepared as in Example 8B (1.5 g, 3.72 mmoles), dimethylamine hydrochloride (334 mg), DCC (845 mg), 1-hydroxybenzotriazole hydrate (553 mg), diisopropyl ethyl amine (5.85 ml), and DMF (100 ml) were combined and stirred at room temperature for 24 hours. The mixture was poured into water and the pH adjusted to 9.8 with 1N NaOH. The mixture was extracted with ethyl acetate and the organic layer dried over K_2CO_3. The solvent was removed under vacuum to yield 1.56 g of desired product The product was passed through a silica column with methanol to provide 800 mg of material. The HCl salt was prepared and filtered to yield 810 mgs.

ms (fd) = 394 M+

Analysis: $C_{25}H_{34}N_2O_2$·HCl: Theory: C, 69.67; H, 8.19; N, 6.50; Found: C, 69.37; H, 8.06; N, 6.40.

EXAMPLE 11

Preparation of 2-[[4-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxo-2-phenylbutyl]amino]-acetic acid ethyl ester monohydrochloride [U-NHCH$_2$C(O)-OCH$_2$CH$_3$·HCl]

The following materials were combined in dry DMF (75 ml): substituted-butanoic acid prepared as in Example 8B (1.5 g, 4 mmole), glycine ethyl ester (558 mg), triethylamine (404 mg), Hobt (540 mg), DCC (824 mg). The above materials were mixed together at room temperature under nitrogen and stirred for three days with the DCC added after solubilization of the solids. The reaction was then filtered and evaporated to dryness. The residue was solubilized in ethyl acetate, washed one time with water and dried over K_2CO_3. The solvent was evaporated to provide 800 mg of solid product. The product was subjected to column chromatography eluting with a gradient of ethyl acetate to a 9:1 (v:v) ethyl acetate-methanol mixture to provide 400 mg of a semisolid material. This was converted to HCl salt to provide 270 mg of white solid.

m.p. = 102°-107° C.

ms (fd) = 452 M+, 453 M+ + 1

Analysis: $C_{27}H_{36}N_2O_4$·HCl Theory: C, 66.31; H, 7.63; N, 5.73; Found: C, 65.99; H, 7.75; N, 5.92.

EXAMPLE 12

Preparation of 2-[[4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-phenyl-1-oxobutyl]amino]ethanoic acid monohydrate. [U-NHCH$_2$C(O)OH·H$_2$O]

Ethyl ester prepared as in Example 11 (1.6 g, 3.5 mmole) and lithium hydroxide (440 mg) were combined in 60 ml of a mixture of tetrahydrofuran, methanol, and water (v:v:v, 3:1:1) and stirred at room temperature. After three hours the mixture was poured into 100 ml of a 10 weight percent aqueous solution of HCl. The mixture was then extracted with a butanol/toluene (v:v, 3:1) solution. The organic layer was backwashed one time with water, dried over K_2CO_3 and the solvent evaporated under vacuum to yield 1.51 g of solid product. The product was subjected to column chromatography eluting with a gradient of ethyl acetate/methanol (9:1, v:v) to ethyl acetate/methanol (1:1, v:v) under nitrogen pressure providing 360 mg of product as a white solid. m.p. = 145°-150° C. with decomposition

ms (fd) = 424 M+

Analysis $C_{25}H_{32}N_2O_4·H_2O$: Theory: C, 67.85; H, 7.74; N, 6.33; Found: C, 67.55; H, 7.87; N, 6.05.

EXAMPLE 13

Preparation of N-(methyl)-2-[[4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-phenyl-1-oxobutyl]amino]acetamide monohydrochloride. [U-NHCH$_2$C(O)-NHCH$_3$·HCl]

U-NHCH$_2$C(O)OCH$_2$CH$_3$·HCl (400 mg) prepared as in Example 11, methylamine (10 ml, 40% in water), methanol (5 ml) were mixed together and stirred at room temperature overnight. The solvent was removed to provide 392 mg of an oil which was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1). 225 mg of a semisolid was recovered. The HCl salt was prepared and dried to provide 220 mg of white solid.

m.p. = 115°-119° C.

Analysis for $C_{26}H_{35}N_3O$·HCl Theory: C, 65.88; H, 7.66; N, 8.86; Found: C, 65.63; H, 7.47; N, 8.70.

EXAMPLE 14

Preparation of trans-N-(2-amino-2-oxoethyl)-4-[3,4-dimethyl-4-(3-hydroxyphenyl)-1-piperidinyl]-2-phenylbutanamide monohydrochloride monohydrate. [U-NHCH$_2$C(O)NH$_2$·HCl·H$_2$O]

The procedure of 13 was followed with product from Example 11 (400 mg), ammonium hydroxide (10 ml, 28%), and methanol (5 ml) to yield 390 mg of a semisolid. This product was subjected to column chromatography eluting with a gradient of ethyl acetate/methanol (v:v, 9:1) to ethyl acetate/methanol (v:v, 1:1). The solvent was removed to yield 240 mg of solid. ms (fd) = 423 M+ and 424 + + 1

The HCl salt was prepared and dried to provide 200 mg of a white solid.

m.p. = 128°-132° C.

Analysis for $C_{25}H_{33}N_3O_3$·HCl·H$_2$O: Theory: C, 62.81; H, 7.59; N, 8.79; Found: C, 63.04; H, 7.74; N, 8.54.

EXAMPLE 15

Preparation of N-ethyl-2-[[4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]]-2-phenyl-1-oxobutylamino]-acetamide monohydrochloride monohydrate. U-$NHCH_3C(O)$-$NHCH_2CH_3$·HCl·H_2O]

The same procedure as in Example 13 was followed using the product from the procedure of Example 11 (400 mg) and ethylamine (20 ml, 70% in H_2O) except the reaction was run for 3.5 days. 400 mg of an oil was recovered. This was subjected to column chromatography eluting with a gradient of ethyl acetate to methanol providing 250 mg of a solid.

ms (fd)=451 M+ and 452 M+ +1

The HCl salt was prepared and dried to provide 200 mg of solid.

m.p.=95°-105° C. (foam)

Analysis for $C_{27}H_{37}N_3O_3$·HCl H_2O: Theory: C, 64.08; H, 7.97; N, 8.30; Found: C, 64.37; H, 7.78; N, 8.19.

EXAMPLE 16

Preparation of 3-[[2-cyclohexyl-4-[4-(3-hydroxypheny)-3,4-dimethyl-1-piperidinyl]-1-oxobutyl]amino]proprionic acid ethyl ester monohydrochloride. [G-$NH(CH_2)_2C(O)OCH_2CH_3$·HCl]

The butanoic acid (G-OH] prepared as in Example 9B (1.45 g, 3.9 mmole), ethyl-3-aminopropionate (600 mg), triethylamine (394 mg) and Hobt (527 mg) were combined in dry DMF (75 ml) followed by the addition of DCC (308 mg). The mixture was stirred at room temperature for 64 hours under nitrogen, evaporated to dryness, and the residue dissolved in ethyl acetate. The ethyl acetate layer was washed two times with water, dried over K_2CO_3 and then evaporated to dryness to yield 2.16 g of material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate/hexane (v:v, 1:1) to ethyl acetate. Removal of solvent provided 1.35 g of product with a mass spec of 472 M+ and 473 M+ +1. The HCl salt was prepared and dried to provide 1.5 g of white solid.

m.p.=117°-122° C.

Analysis: $C_{28}H_{44}N_2O_4$·HCl Theory: C, 66.21 H, 9.03 N, 5.31; Found: C, 66.05; H, 8.91; N, 5.40.

EXAMPLE 17

Preparation of N-(3-amino-3-oxopropyl)-4[3,4-dimethyl-4-(3-hydroxyphenyl)-1-piperidinyl]-2-butanamide monohydrochloride. [G-$NH(CH_3)_2C(O)NH_2$·HCl]

The ethyl propionate (HCl salt) G-$NH(CH_2)_2$-$C(O)OCH_2CH_3$] prepared as in Example 16 (400 mg) and ammonium hydroxide (25 ml, 28% in H_2O) were mixed and stirred at room temperature overnight. The mixture was evaporated to dryness and the residue was taken into butanol/toluene (v:v, 3:1) and water. The pH was adjusted to 9.8 with 1N NaOH and the layers were separated. The organic layer was washed one time with water, dried over K_2CO_3 and then evaporated under vacuum to yield 350 mg of material. This material was subjected to column chromatography eluting with ethyl acetate to methanol gradient. Removal of the solvent provided 200 mg of product with a mass spec of 443 M+ and 444 M+ +1. The HCl salt was prepared and dried to yield 160 mg of white solid.

m.p.=119°-124° C. (with decomposition)

Analysis for $C_{26}H_{41}N_3O_3$·HCl: Theory: C, 65.05; H, 8.82; N, 8.75; Found: C, 64.76; H, 8.75; N, 8.38.

EXAMPLE 18

Preparation of N-[3-(methylamino)-3-oxopropyl]-4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-cyclohexylbutanamide monohydrochloride. [G-$NH(CH_2)_2$-$C(O)NHCH_3$·HCl].

The procedure of Example 17 was followed with the ethyl propionate product (HCl salt) prepared as in Example 16 (450 mg), methylamine (25 ml, 40% in H_2O) and dioxane (10 ml) to provide 470 mg of material. This material was subjected to column chromatography eluting with ethyl acetate/methanol (v:v, 9:1) to methanol gradient. Solvent was removed to provide 290 mg of product.

ms (fd)=458 M+, 459 M+ +1

The HCl salt was prepared and dried to provide 275 mg of a white solid.

m.p.=124°-130° C.

Analysis for $C_{27}H_{43}N_3O_3$·HCl: Theory: C, 65.63; H, 8.98; N, 8.50; Found: C, 65.42; H, 9.01; N, 8.29.

EXAMPLE 19

Preparation of trans-N-[2-ethoxy-2-oxoethyl-4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-cyclohexylbutanamide hydrochloride. [G-$NHCH_2C(O)OCH_2$-CH_3·HCl]

The butanoic acid prepared as in Example 9B (900 mg), glycine ethyl ester·HCl (348 mg), Hobt (338 mg), TEA (253 mg), and DCC (515 mg) were combined and the reaction was stirred for 72 hours at room temperature. The mixture was evaporated to dryness under vacuum. The residue was dissolved into water/ethyl acetate and the pH of the water layer was adjusted to 9.8 with 1N sodium hydroxide. The layers were separated and the organic layer washed with water, dried over K_2CO_3 and the solvent was evaporated under vacuum to yield 1.25 g of oily material. This material was subjected to column chromatography eluting with ethyl acetate. Solvent removal provided 720 mg of product. This material was converted to the HCl salt.

ms (fd)=458 M+

m.p.=98°-101° C.

Analysis: $C_{27}H_{42}N_2O_4$·Hcl Theory: C, 65.50; H, 8.75; N, 5.66; Found: C, 65.84; H, 8.81; N, 5.87.

EXAMPLE 20

Preparation of N-(2-amino-2-oxoethyl)-4-[4-(3hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-cyclohexylbutanamide hydrochloride monohydrate. [G-$NHCH_2C(O)$-NH_2·HCl·H_2O]

The procedure of Example 17 was followed with the butanamide product (HCl salt) prepared as in Example 19 (400 mg), ammonium hydroxide (25 ml, 28% in water) and methanol (10 ml) with the mixture being stirred overnight. 350 mg of material was recovered and subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 1:1). Removal of solvent yielded 220 mg of product with a mass spec of 429 M+ and 430 M+ +1. The HCl salt was prepared and dried to yield 170 mg of white solid.

m.p.=129°-134° C.

Analysis for $C_{25}H_{39}N_3O_3 \cdot HCl \cdot H_2O$: Theory: C, 62.03; H, 8.75; N, 8.68; Found: C, 62.46; H, 8.53; N, 8.20.

EXAMPLE 21

Preparation of N-[2-(methylamino)-2-oxoethyl]-4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-cyclohexyl butanamide hydrochloride. [G-$NHCH_2C(O)NHCH_3 \cdot HCl$]

The procedure of Example 17 was followed with the butanamide product [G-$NHCH_2C(O)OCH_2CH_3$] (HCl salt) prepared as in Example 19 (600 mg) and methylamine (35 ml, 40% in H_2O) to yield 580 mg of material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 1:1) providing 300 mg of product. The HCl salt was prepared and dried to yield 275 mg of a white solid.

ms (fd)=444 M^+

m.p.=119°–12° C.

Analysis for $C_{26}H_{41}N_3O_3 \cdot HCl \cdot H_2O$: Theory: C, 62.68; H, 8.90; N, 8.44; Found: C, 62.39; H, 8.64; N, 8.23.

EXAMPLE 22

Preparation of N-[2-(ethylamino)-2-oxoethyl]-4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-cyclohexyl butanamide hydrochloride. [G-$NHCH_2C(O)NHCH_2CH_3 \cdot HCl$]

The procedure of Example 17 was followed with the butanamide (HCl salt) product prepared as in Example 19 (600 mg) and ethylamine (30 ml, 70%) to yield 660 mg of material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 1:1). Solvent removal provided 320 mg of product. The HCl salt was prepared and dried to yield 350 mg of white solid.

ms (fd)=458 M^+

m.p.=123°–126° C.

Analysis for $C_{27}H_{43}N_3O_3 \cdot HCl \cdot H_2O$: Theory: C, 63.31; H, 8.98; N, 8.21; Found: C, 63.53; H, 8.92; N, 8.47.

EXAMPLE 23

Preparation of 4-[2-cyclohexyl-4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxobutyl]amino]-butanoic acid ethyl ester monohydrochloride monohydrate [G-$NH(CH_2)_3C(O)OCH_2CH_3 \cdot HCl \cdot H_2O$]

The butanoic acid product prepared as in Example 9B (1.5 g), ethyl-4-aminobutanoate hydrochloride (671 mg), TEA (405 mg) Hobt (540 mg) were combined in dry DMF (150 ml). DCC (824 mg) was added last. The mixture was stirred 64 hours at room temperature under nitrogen. After evaporation to dryness, the residue was taken into ethyl acetate which was washed two times with water and dried over K_2CO_3. Evaporation to dryness yielded 2.23 g of residue. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to methanol/ethyl acetate (v:v, 9:1). Removal of solvent provided 1 g of product.

ms (fd)=486 M^+ and 487 $M^+ + 1$ 350 mg of this product was converted to HCl salt to yield 300 mg of white solid after drying.

m.p.=76°–79° C.

Analysis for $C_{29}H_{46}N_2O_4 \cdot HCl \cdot H_2O$ Theory: C, 64.30; H, 9.05; N, 5.18; Found: C, 63.90; H, 9.01; N, 5.12.

EXAMPLE 24

Preparation of N-methyl-4-[[4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-cyclohexyl-1-oxobutyl]amino]butanamide monohydrochloride monohydrate. G-$NH(CH_2)_3C(O)NHCH_3 \cdot HCl \cdot H_2O$]

Butanoate product prepared as in Example 23 (450 mg) and methylamine (15 ml, 40% in water) were mixed and stirred at room temperature for three hours. Evaporation of the reaction mixture to dryness provided a residue which was dissolved into butanol-toluene (v:v, 3:1) and water. The water layer was taken to a pH of 9.8 with 1N NaOH and the layers separated. The organic layer was washed one time with water, dried over K_2CO_3 and the solvent removed to yield 470 mg of a viscous oil. This material was column chromatographed eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 1:1) providing 250 mg of product. The HCl salt was prepared and dried to yield 250 mg of white solid.

m.p.=78°–84° C. (foam)

Analysis for $C_{28}H_{45}N_3O_3 \cdot HCl \cdot H_2O$: Theory: C, 63.91; H, 9.20; N, 7.99; Found: C, 64.21; H, 8.95; N, 7.83.

EXAMPLE 25

Preparation of 3-[[2-cyclohexyl-4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxobutyl]amino]propanoic acid phenylmethyl ester hydrochloride monohydrate. [G-$NH(CH_2)_2C(O)OCH_2(C_6H_5) \cdot HCl \cdot H_2O$]

The butanoic acid of Example 9B (900 mg) [G-OH], β-alanine benzyl ester.para-tosylate (878 mg), Hobt (338 mg), DCC (515 mg) and TEA (253 mg) were combined in DMF (100 ml) and stirred for 64 hours at room temperature. The solution was evaporated to dryness under vacuum. The residue was partitioned between ethyl acetate and water and the water layer was adjusted to a pH of 9.8 with 1N NaOH. The layers were separated and the organic layer washed one time with water, dried over K_2CO_3 and evaporated to yield 1.57 g of material. This material was column chromatographed eluting with a gradient of ethyl acetate to ethyl acetate-methanol (1:1, v:v) providing 620 mg of product. This was converted to HCl salt.

ms (fd)=534 M^+ and 535 $M^+ + 1$

m.p.=87°–90° C.

Analysis for $C_{33}H_{46}N_2O_4 \cdot HCl \cdot H_2O$: Theory: C, 67.23; H, 8.39; N, 4.75; Found: C, 67.31; H, 8.43; N, 5.03.

EXAMPLE 26

Preparation of 3-[4-[3,4-dimethyl-4-(-3-hydroxyphenyl)-1-piperidinyl]-2-cyclohexyl-1-oxobutylamino]-propanoic acid monohydrate [G-$NH(CH_2)_2C(O)OH \cdot H_2O$]

Propanoate prepared in Example 25 (1.5 g) was dissolved in ethanol and 5% Pd on carbon was added and the solution was stirred overnight under 60 Psi hydrogen pressure. The mixture was filtered and evaporated to dryness to yield 1.43 g of material. This material was triterated in ethyl acetate and filtered to yield 1.11 g of product.

ms (fd)=444 M^+ to 445 $M^+ + 1$

m.p.=90°–93° C.

Analysis for $C_{26}H_{40}N_2O_4 \cdot H_2O$: Theory: C, 67.53; H, 9.09; N, 6.06; Found: C, 67.77; H, 8.96; N, 5.90.

EXAMPLE 27

Preparation of
2-[[2-cyclohexyl-4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxobutyl]amino]-acetic acid monohydrate [G-$NHCH_2C(O)OH \cdot H_2O$]

Butanamide (HCl salt) [G-$NHCH_2C(O)OCH_2CH_2 \cdot HCl$] prepared as in Example 19 (400 mg), 6N HCl (30 ml), and dioxane (30 ml) were combined and refluxed for four hours. The mixture was evaporated to dryness and the residue was partitioned between butanol-toluene (v:v, 3:1) and water. The pH of the water was adjusted to 9.8 with ammonium hydroxide and the layers were separated. The organic layer was dried over $MgSO_4$ and evaporated to provide 540 mg of material. This material was subjected to column chromatography eluting with ethyl acetate/methanol (v:v, 1:1). Removal of solvent provided 172 mg of product.

ms (fd)=430 M^+ and 431 $M^+ + 1$

m.p.=148°–153° C.

Analysis for $C_{25}H_{38}N_2O_4 \cdot H_2O$: Theory: C, 66.94; H, 8.90; N, 6.24; Found: C, 66.64; H, 8.84; N, 5.88.

EXAMPLE 28

Preparation of
4-[[2-cyclohexyl-4-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxobutyl]amino]-butanoic acid monohydrate [G-$NH(CH_2)_3C(O)OH \cdot H_2O$]

The butanoate prepared using the procedure of Example 23 (550 mg), 6N HCl (20 ml) and dioxane (20 ml) were combined and refluxed for two hours. The reaction mixture was evaporated to dryness. The residue was taken into water and butanol-toluene (v:v, 3:1). The pH of the water layer was adjusted to 9.8 using ammonium hydroxide and the layers were separated. The organic layer was washed one time with water, dried over $MgSO_4$ and evaporated to provide 490 mg of dry material. This material was subjected to column chromatography eluting with a gradient of hexane/ethyl acetate (v:v, 1:1) to ethyl acetate. Solvent removal provided 300 mg of product.

ms (fd)=458 M^+

m.p.=113°–118° C. (with decomposition)

Analysis for $C_{27}H_{42}N_2O_4 \cdot H_2O$: Theory C, 67.99; H, 9.23; N, 5.88; Found: C, 67.85; H, 8.88; N, 5.65.

EXAMPLE 29

Preparation of
2-[[3-[4-(3-hydroxyphenyl-3,4-dimethyl-1-piperidinyl]-2-cyclohexylmethyl-1-oxopropyl]amino]acetic acid ethyl ester monohydrochloride.
[M-$NHCH_2C(O)OCH_2CH_3 \cdot HCl$]

The propanoic acid prepared as in Example 5B (1.0 g), Hobt (384 mg), triethylamine (0.4 ml), glycine ethyl ester·HCl (374 mg), dimethylformamide (50 ml) and DCC (586 mg) were combined and stirred for four days at room temperature. Solvent was removed and the residue was passed through a silica column eluting with ethyl acetate. Removal of solvent yielded 990 mg of product. The HCl salt was prepared and triturate in ethyl ether and filtered to yield a white solid.

m.p. 97°–107° C.

Analysis for $C_{27}H_{42}N_2O_4 \cdot HCl$: Theory: C, 65.50; H, 8.75; N, 5.66; Found: C, 65.73; H, 8.50; N, 5.76.

EXAMPLE 30

Preparation of
2-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(cyclohexylmethyl)-1-oxopropyl]-amino]acetic acid monohydrate [M-$NHCH_2C(O)OH \cdot H_2O$]

The product of Example 29 (1.08 g), lithium hydroxide (302 mg), and water/methanol/THF (20 ml, 1:1:3) were combined and stirred at room temperature for four hours. The reaction mixture was poured into 10% HCl/water and the mixture was extracted with butanol-toluene (v:v, 3:1). The organic layer was washed one time with water, dried over $MgSO_4$, and evaporated to provide 1.05 g of material. This material was subjected to column chromotography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (1:1) providing 510 mg of solid material.

m.p.=112°–116° C.

ms (fd)=430 M^+ to 431 $M^+ + 1$

Analysis for $C_{25}H_{38}N_2O_4 \cdot H_2O$: Theory: C, 66.90; H, 8.92; N, 6.25; Found: C, 67.10; H, 8.77; N, 6.24.

EXAMPLE 31

Preparation of
N-ethyl-2-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(cyclohexylmethyl)-1-oxo-propyl-]amino]acetamide monohydrochloride monohydrate
M-$NHCH_2C(O)NHCH_2CH_3 \cdot HCl \cdot H_2O$]

The procedure of Example 17 was followed with the ester of Example 29 (400 mg) and ethylamine (20 ml, 70% in H_2O) to yield 390 mg of material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1). Solvent removal yielded 200 mg of product. ms (fd)=457 M^+ and 458 $M^+ + 1$ The HCl salt was prepared and dried at 60° C. to provide 173 mg of white solid.

m.p.=137°–140.5° C.

Analysis for $C_{27}H_{43}N_3O_3 \cdot HCl\ H_2O$: Theory: C, 63.32; H, 9.05; N, 8.21; Found: C, 63.12; H, 8.82; N, 7.95.

EXAMPLE 32

Preparation of
N-[2-methylamino-2-oxoethyl]-3-[4-(3-hydroxphenyl)-3,4-dimethyl(-1-piperidinyl]-2-cyclohexylmethyl-propanamide monohydrochloride
[M-$NHCH_2C(O)NHCH_3 \cdot HCl$]

The procedure of Example 31 was followed with the propanamide prepared as in Example 29 (400 mg) and methylamine (20 ml, 40% in water) to provide 380 mg of material which was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1). Solvent removal provided 210 mg of product.

ms (fd)=443 M^+, 444 $M^+ + 1$ The HCl salt was prepared and dried to provide 171 mg of solid.

m.p.=131°–135° C.

Analysis for $C_{26}H_{41}N_3O_3 \cdot HCl$: Theory: C, 65.0S; H, 8.82; N, 8.75; Found C, 65.37; H, 8.81; N, 8.88.

EXAMPLE 33

Preparation of
2-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(cyclohexylmethyl)-1-oxophenyl]amino]acetamide monohydrochloride [M-$NHCH_2C(O)NH_2$·HCl]

The procedure of Example 31 was followed with the propanamide prepared as in Example 29 (400 mg) and ammonium hydroxide (20 ml, 28% in H_2O) except the mixture was stirred for three days and then evaporated to dryness under vacuum. 350 mg of material were recovered which was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1). Solvent removal provided 240 mg of product.

ms (fd)=429 M^+ and 430 $M^+ + 1$ The HCl salt was prepared and dried at 60° C. to provide 186 mg of solid.

m.p.=140°–144° C.

Analysis for $C_{25}H_{39}N_3O_3$·HCl: Theory: C, 64.43; H, 8.65; N, 9.02; Found: C, 64.69; H, 8.86; N, 8.93.

EXAMPLE 34

Preparation of
3-[[2-(cyclohexylmethyl)-1-oxo-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]propyl]-amino]-propanoic acid phenylmethyl ester monohydrochloride [M-$NH(CH_2)_2C(O)OCH_2(CH_6H_5)$·HCl]

Propanoic acid product of the Example 5B procedure (809 mg), β-alanine benzyl ester-p-tosylate (760 mg), Hobt (293 mg), TEA (0.364 ml), DCC (447 mg), and DMF (80 ml) were combined and stirred at room temperature for three days. The mixture was stripped to dryness and diluted with butanol-toluene (v:v, 3:1) and water. The pH was adjusted to 9.8 with IN NaOH and the organic layer was separated. The organic layer was dried over K_2CO_3 and the solvent removed. The residue was diluted with ethyl acetate and passed through a column of silica gel. The recovered product was converted to the HCl salt and triterated with ethyl ether and filtered to provide 600 mg of white solid.

m.p.=80°–90° C.

Analysis for $C_{33}H_{46}N_2O_4$·HCl: Theory: C, 69.39; H, 8.29; N, 4.90 ; Found: C, 69.50; H, 8.42; N, 4.93.

EXAMPLE 35

Preparation of
3-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(cyclohexylmethyl)-1-oxopropyl]-amino]propanoic acid hydrochloride [M-$NH(CH_2)_2C(O)OH$·HCl]

The propanoic acid ester product of Example 34 (950 mg) was contacted with 5% Pd on carbon in ethanol under 60 pounds per square inch hydrogen pressure. The solvent was stripped and the residue passed through a silica column eluting with methanol to give 760 mg of product. This was converted to the HCl salt to provide 404 mg of white solid. m.p.=115°–120° C.

Analysis for $C_{26}H_{40}N_2O_4$·HCl: Theory: C, 6%.91; H, 8.59; N, 5.82 ; Found C, 6S.04; H, 8.58; N, 5.90.

EXAMPLE 36

Preparation of
3-[[2-(cyclohexylmethyl)-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxo-propyl]amino]propanoic acid ethyl ester monohydrochloride [M-$NH(CH_2)_2C(O)OCH_2CH_3$·HCl]

Propanoic acid product of the procedure of Example 5B (1 g), β-alanine ethyl ester hydrochloride (400 mg) triethylamine (263 mg) Hobt (351 mg), were combined in dry dimethylformamide (75 ml) and then DCC (536 mg) was added. These reactants were mixed together at room temperature under nitrogen for 3 days. The reaction mixture was filtered and evaporated to dryness. The residue was dissolved in ethyl acetate, which was washed one time with water, dried over K_2CO_3 and evaporated to provide 1.74 g of material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate/hexane (v:v, 1:1) to ethyl acetate. Removal of the solvent provided 520 mg of solid which was coverted to the HCl salt to provide 270 mg of solid.

m.p.=86°–89° C.

ms (fd)=472 M^+ and 473 $M^+ + 1$

Analysis for $C_{28}H_{44}N_2O_4$·HCl: Theory C, 66.05; H, 8.91; N, 5.51; Found: C, 6S.86; H, 8.72; N, 5.81.

EXAMPLE 37

Preparation of N-[3-(methylamino)-3-oxopropyl]-3-[3,4-dimethyl-4-(3-hydroxyphenyl)-1-piperidinyl]-2-cyclohexylmethylpropanamide monohydrochloride [M-$NH(CH_2)_2C(O)NHCH_2CH_3$·HCl]

The procedure of Example 17 was followed with the propanoic acid ester product of the procedure of Example 36 (450 mg) and ethylamine (20 ml, 70% in H_2O) to provide 440 mg of material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1) providing 250 mg of product.

ms (fd)=471 M^+ and 472 $M^+ + 1$ This product was coverted to the HCl salt and dried to provide 225 mg of solid.

m.p.=109°–113° C.

Analysis for $C_{28}H_{45}N_3O_3$·HCl Theory: C, 66.18: H, 9.13: N, 8.27; Found: C, 66.36; H, 9.29 N, 8.53.

EXAMPLE 38

Preparation of
3-[[1-oxo-2-cyclohexylmethyl)-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]propyl]-amino]propanamide hydrochloride [M-$NH(CH_2)_2C(O)NH_2$·HCl]

Propanoic acid ethyl ester prepared as in Example 36 (300 mg) and ammonium hydroxide (15 ml, 28% in H_2O) were combined and stirred at room temperature for three days. Upon evaporating to dryness under vacuum, 270 mg of material were recovered. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1). Removal of solvent provided 170 mg of product.

ms (fd)=443 M^+ and 444 $M+1$ This product was converted to the HCl salt and dried to provide 108 mg of solid.

m.p.=101°–105° C.

Analysis for $C_{26}H_{41}N_3O_3$·HCl Theory: C, 65.04; H, 8.82; N, 8.75; Found: C, 65.29; H, 9.07; N, 8.87.

EXAMPLE 39

Preparation of
4-[[3-[3,4-dimethyl-4-(3-hydroxyphenyl)-1-piperidinyl]-2-(cyclohexhymethyl)-1-oxopropyl]-amino]butanoic acid ethyl ester monohydrochloride [MN$H(CH_2)_3C(O)OCH_2CH_3$·HCl]

The propanoic acid product of the Example 5B procedure (809 mg), ethyl-4-aminobutyrate·HCl (399 mg),

HOBT (293 mg), TEA (0.364 ml), DCC (447 mg) were combined in DMF (80 ml) and stirred for 72 hours at room temperature. The reaction mixture was evaporated to dryness under vacuum. The recovered material was subjected to column chromatography eluting with ethyl acetate/hexane (1:1) to yield 610 mgs after solvent removal. This material was converted to the HCl salt yielding 540 mg of white solid.

m.p.=70°-85° C. Analysis: $C_{29}H_{46}N_2O_4$·HCl Theory: C, 66.58; H, 9.06; N, 5.35; Found: C, 66.49; H, 9.05; N, 5.30.

EXAMPLE 40

Preparation of
4-[[1-oxo-2-(cyclohexylmethyl)-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]propyl]-amino]-butanamide hydrochloride
[M-$NH(CH_2)_3C(O)NH_2$·HCL]

The procedure of Example 17 was followed with the butanoic acid ester of Example 39 (300 mg) and ammonium hydroxide (15 ml, 28%), with the mixture being stirred for three days. 260 mg of material were recovered and subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (9:1, v:v). Solvent evaporation under vacuum provided 100 mg of product.

ms (fd)=457 M+

The product was converted to the HCl salt and dried to provide 63 mg of solid.

m.p.=90°-94° C.

Analysis for $C_{27}H_{43}N_3O_3$·HCl: Theory C, 65.63; H, 8.98; N, 8.50; Found: C, 65.98; H, 8.98; N, 8.35.

EXAMPLE 41

Preparation of
N-[4-(methylamino)-4-oxobutyl]-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-cyclohexylmethylpropanamide monohydrochloride
[M-$NH(CH_2)_3C(O)NHCH_3$·HCl]

The procedure of Example 17 was followed with butanoic acid ethyl ester prepared as in Example 39 (400 mg) and methylamine (20 ml, 40% in H_2O), except the mixture was stirred overnight. 350 mg of material were recovered and subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1) to provide 270 mg of product.

ms (fd)=471 M+ and 472 M++1 This product was converted to the HCl salt and dried to provide 250 mg of white solid.

m.p.=89°-94° C.

Analysis for $C_{28}H_{45}N_3O_3$·HCl: Theory: C, 66.18; H, 9.13; N, 8.29; Found: C, 65.97; H, 9.12; N, 8.08.

EXAMPLE 42

Preparation of
N-[4-(ethylamino)-4-oxobutyl]-3-[4-(3--hydroxyphenyl)-3,4-dimethyl-1-piperidinyl[-2-cyclohexyl-methyl propanamide monohydrate hydrochloride
[M-$NH(CH_2)_3C(O)NHCH_2CH_3$·HCl·H_2O]

The procedure of Example 17 was followed with the butanoic acid ethyl ester product of the procedure of Example 39 (400 mg) in ethylamine (20 ml, 70% in H_2O) to provide 340 mg of material which was subjected to column chromatoqraphed eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1). Solvent removal provided 200 mg of product.

ms (fd)=485 M+, 486 M++1 This was converted to the HCl salt and dried to provide 210 mg of white solid.

m.p=95°-100° C.

Analysis for $C_{29}H_{47}N_3O_3$·HCl·H_2O: Theory: C, 64.48; H, 9.33; N, 7.78; Found: C, 64.19; H, 9.14; N, 7.68.

EXAMPLE 43

Preparation of
2-[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxo-2-(phenylmethyl)propyl]-amino]acetic acid ethyl ester hydrochloride [X-OCH_2CH_3·HCl]

Propanoic acid [Z-OH] from the procedure of Example 4B (1.23 g), Glycine ethyl ester·HCl (486 mg), Hobt (473 mg), TEA (0.487 ml) were combined in DMF (100 ml) and cooled to 0° C. To this was added DCC (719 mg) and the mixture allowed to warm to room temperature. The mixtured was stirred for three days at room temperature, filtered and the solvent removed under vacuum. The residue was diluted with butanol-toluene (v:v, 3:1) and water. The pH was adjusted to 9.8 with ammonium hydroxide. The organic layer was separated and dried over K_2CO_3 and the solvent was removed. The residue was passed through a silica column eluting with ethyl acetate/hexane (v:v, 3:1). The solvent was removed to yield 1.17 g of product. This was converted to the HCl salt to provide 1.0 g of white solid.

m.p.=75°-87° C.

Analysis for $C_{27}H_{36}N_2O_4$·HCl: Theory: C, 66.31; H, 7.63; N, 5.72; Found: C, 66.06; H, 7.55; N, 5.80.

EXAMPLE 44

Preparation of
2-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxo-2-(phenylmethyl)propyl]-amino]acetic acid monohydrate [X-OH·H_2O]

Acetic acid ester prepared as in Example 43 (HCl salt) (600 mg) was dissolved in ethanol (20 ml) and 1N NaOH (2.6 ml) was added. The mixture allowed to stir at room temperature for two hours and the solvent removed under reduced pressure The residue was taken into H_2O and the pH adjusted to 7 with 1N HCl. The H_2O was removed under vacuum and the residue dried. The residue was slurried in ethanol, filtered, and the solvent removed to yield 500 mg of material. This material was passed through a silica column eluting with ethyl acetate/methanol (3:2). The solvent was removed to yield 450 mg of material. This was recrystallized from an ethyl acetate/methanol (1:1) mixture to provide 378 mg of final product as a white solid.

m.p.=161°-165° C.

Analysis for $C_{25}H_{32}N_2O_4$·H_2O: Theory: C, 68.16; H, 7.32; N, 6.36 ; Found: C, 68.08; H, 7.30; N, 6.22.

EXAMPLE 45

Preparation of
N-ethyl-2-[[2-(phenylmethyl-)-1-oxo-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]propyl]-amino]-ethanamide [X-$NHCH_2CH_3$].

Acetic acid ester product prepared as in Example 43 (HCl salt) (300 mg) was combined with ethylamine (50 ml, 70%) and stirred for one hour. The solvent evaporated and the residue dissolved in ethyl acetate. The organic layer was washed with water, dried over K_2CO_3 and the solvent removed to provide 240 mg of a solid.

ms (fd)=451 M+

Analysis for $C_{27}H_{37}N_3O_3$ Theory: C 71.81 H 8.29 N 9.30; Found: C 71.96 H 8.18 N 9.49.

EXAMPLE 46

Preparation of N-(2-amino-2-oxoethyl)-3-[3,4-dimethyl-4-(3-hydroxyphenyl)-1-piperidinyl]-2-phenylmethyl propanamide monohydrochloride monohydrate [$XNH_2 \cdot HCl \cdot H_2O$]

Acetic acid ester product prepared as in Example 43 (HCl salt) (500 mg), ammonium hydroxide (10 ml, 28%) and methanol (5 ml) were combined and stirred at room temperature overnight. The mixture was evaporated to dryness under vacuum and the residue was partitioned between butanol-toluene (v:v, 3:1) and water. The pH of the water layer was adjusted to 9.8 with 1N NaOH and the layers separated. The organic layer was washed one time with water and dried over K_2CO_3. The solvent was evaporated to yield 470 mg of a viscous oil. This oil was passed over a silica column eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1). Removal of solvent provided 270 mg of an oil.

ms (fd)=423 M^+, 424 $M^+ + 1$

This product was converted to the HCl salt to provide 250 mg of white solid which was triturated in ethyl acetate and filtered to yield 230 mgs white solid.

m.p.=134°-137° C.

Analysis for $C_{25}H_{34}N_3O_3 \cdot HCl \cdot H_2O$: Theory: C, 62.81; H, 7.59; N, 8.79; Found: C, 62.58; H, 7.31; N, 8.59.

EXAMPLE 47

Preparation of N,N-dimethyl-2-[[3-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(phenylmethyl)-1-oxypropyl-]amino]acetamide monohydrochloride monohydrate X-$N(CH_3)_2 \cdot HCl \cdot H_2O$]

The procedure of Example 46 was followed with acetic acid ester (HCl salt) product of the Example 43 procedure (500 mg), dimethylamine (10 ml, 40 wt. % in water) and methanol (5 ml) with the reaction mixture stirred for two hours. 350 mg of material were recovered which was passed through a silica column eluting with ethyl acetate. 230 mg of product were recovered.

ms (fd)=451 $M^+ + 1$ This material was converted to the HCl salt to provide 200 mg of white solid.

m.p.=119°-123° C.

Analysis for $C_{27}H_{37}N_3O_3 \cdot HCl \cdot H_2O$: Theory: C, 64.28; H, 7.85; N, 8.61; Found: C, 64.57; H, 7.68; N, 8.53.

EXAMPLE 48

Preparation of N-(1-methylethyl)-2-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(phenylmethyl)-1-oxopropyl-]amino]acetamide hydrochloride monohydrate X-$NHCH(CH_3)_2 \cdot HCl \cdot H_2O$]

Acetic acid ester (HCl salt) product of the procedure of Example 43 (750 mg) [X-OCH_2CH_3], 2-aminopropane (106 mg), Hobt (243 mg) were mixed in DMF (50 ml) followed by the addition of DCC (371 mg). This mixture was stirred at room temperature for 64 hours under nitrogen. The mixture was evaporated to dryness and the residue dissolved in ethyl acetate, which was then washed two times with water and dried over K_2CO_3. The solvent was removed to provide 880 mg of material which was passed through a silica column eluting with ethyl acetate. Solvent Evaporation provided 450 mg of product.

ms (fd)=465 M^+, and 466 $M^+ + 1$ The HCl salt was formed and the white solid dried at 60° C.

m.p.=124°-128° C.

Analysis for $C_{28}H_{39}N_3O_3 \cdot HCl \cdot H_2O$: Theory: C, 64.66; H, 8.14; N, 8.08; Found: C, 64.83; H, 8.30; N, 8.34.

EXAMPLE 49

Preparation of N-2-propylamino-2-oxoethyl]-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-phenylmethyl propanamide monohydrate hydrochloride. [$XNH(CH_2)_2CH_3 \cdot HCl \cdot H_2O$]

Acetic acid ester (HCl salt) prepared as in Example 43 (750 mg), 1-aminopropane (106 mg) and Hobt (243 mg) were combined in DMF (50 ml) followed by the addition of DCC (371 mg) using the procedure of Example 48. 1.2 g of material were obtained and passed through a silica column eluting with ethyl acetate to provide 500 mg of product.

ms (fd)=465 M^+, 466 $M^+ + 1$ This product was converted to the HCl salt and dried to provide 510 mg of white solid.

m.p.=115°-120° C.

Analysis for $C_{28}H_{39}N_3O_3 \cdot HCl \cdot H_2O$: Theory: C, 64.66; H, 8.14; N, 8.08; Found: C, 64.91; H, 7.86; N, 7.97.

EXAMPLE 50

Preparation of N-2-[(2-methylpropyl)amino]-2-oxo-ethyl]-3-[3,4-dimethyl-4-(3-hydroxyphenyl)-1-piperidinyl-2-phenylmethyl propanamide monohydrate hydrochloride [X-$NHCH_2CH(CH_3)_2 \cdot HCl \cdot H_2O$]

The procedure of Example 48 was followed with acetic acid ester (HCl salt) prepared as in Example 43 (600 mg), 2-methyl-1-aminopropane (102 mg), Hobt (189 mg), dry DMF (50 ml) and DCC (288 mg). 940 mg of material were isolated and passed through a silica column eluting with ethyl acetate to provide 300 mg of product.

ms (fd) of 479 M^+.

This product was converted to the HCl salt and dried to provide 210 mg of white solid.

m.p.=107°-110° C.

Analysis for $C_{29}H_{41}N_3O_3 \cdot HCl \cdot H_2O$: Theory: C, 65.21; H, 8.30; N, 7.87; Found: C, 65.51; H, 8.07; N, 7.80.

EXAMPLE 51

Preparation of 2-[[2-(phenylmethyl)-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxopropyl]-amino]ethanoic acid 2-propyl ester monohydrochloride [X-$OCH(CH_3)_2 \cdot HCl$]

Acetic acid ester (HCl salt) prepared as in Example 43 (1.0 g), isopropyl alcohol (20 ml), and 3 angstrom molecular sieve (50 mg) were combined followed by the addition of isopropyl alcohol saturated with gaseous HCl (20 ml). The reaction mixture was refluxed for 48 hours and the solvent removed. The residue was diluted with water and the pH adjusted to 9.8 with TEA. The mixture was extracted with ethyl acetate which was then dried over K_2CO_3. The solvent was removed and the residue passed through a silica column eluting with ethyl acetate. The recovered product was converted to the HCl salt to provide 700 mg of white solid after drying. The solid was triturated in ethyl acetate and filtered to yield 650 mgs of white solid.

m.p.=75°–120° C. (foam):

Analysis for $C_{28}H_{38}N_2O_4$·HCl Theory: C, 66.85; H, 7.81; N, 5.57; Found: C, 66.98; H, 7.64; N, 5.52.

EXAMPLE 52

Preparation of 2-[[2-(phenylmethyl)-1-oxo-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]propyl]amino]-ethanoic acid cyclohexyl ester monohydrochloride [X-O-(CH_6H_{11})·HCl]

To acetic acid ester (HCl salt) prepared as in Example 43 (1.0 g) and 3 angstrom molecular sieve (0.5 g) was added cyclohexanol (20 ml) followed by cyclohexanol saturated with gaseous HCl (20 ml). The mixture was allowed to stir 72 hours at room temperature. The mixture was then heated to 50° C. for 24 hours, cooled, filtered, and stripped to dryness. The resulting material was triturated in hexane. The solvent was removed, the residue dissolved in water, and the pH adjusted to 9.8 with triethylamine. The Product was extracted with ethyl acetate which was then dried over K_2CO_3. The solvent was removed and the residue was passed through a silica column eluting with ethyl acetate/hexane (v:v, 4:1). After removing the solvent, the product was converted to the HCl salt to give 65 mg of white solid.

m.p.=100°–140° C. (foam):

Analysis for $C_{32}H_{44}N_2O_4$·HCl: Theory: C, 68.55; H, 7.98; N, 5.16; Found: C, 68.80; H, 7.82; N, 5.05.

EXAMPLE 53

Preparation of 2-[[2-(phenylmethyl)-1-oxo-3-[4-(3-hydroxyphenyl)-3,%-dimethyl-1-piperidinyl]propylamino]-ethanoic acid cyclohexylmethyl ester monohydrochloride [X-$OCH_2(CH_6H_{11})$·HCl]

Acetic acid ester prepared as in Example 43 (HCl salt) (7S0 mg) and cyclohexylmethanol saturated with Gaseous HCl (20 ml) were combined and heated to 60° C. for 24 hours. The mixture was evaporated to dryness under vacuum. The residue was diluted with water and ethyl acetate and the pH adjusted to 9.8 with triethylamine. The organic layer was separated, and dried over K_2CO_3. The solvent was removed and the residue passed through a silica column eluting with hexane/ethyl acetate (v:v, 1:1). Removal of solvent provided the product which was converted to the HCl salt and triturated in ethyl ether to provide 263 mg of tan solid.

m.p.=140°–155° C. (foam):

Analysis for $C_{32}H_{44}N_2O_4$·HCl: Theory: C, 68.98; H, 8.14; N, 5.03; Found: C, 69.18; H, 8.05; N, 4.83.

EXAMPLE 54

Preparation of 2-[2-(phenylmethyl)-1-oxo-3–4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]propyl]amino]-ethanoic acid 2-methylpropyl ester monohydrochloride [X-$OCH_2CH(CH_3)_2$·HCl]

Acetic acid ester prepared as in Example 43 (HCl salt) (1.0 g), 3 angstrom molecular sieve (0.5 g) and isobutyl alcohol saturated with Gaseous HCl (40 ml) were combined and stirred at room temperature for 72 hours. The mixture was then heated to 50° C. for 24 hours. The reaction was filtered and the filtrate was stripped to dryness. The resulting residue was diluted with water and the pH adjusted to 9.8 with triethylamine. The product was extracted into ethyl acetate and the organic layer dried over K_2CO_3. The solvent was removed and the residue passed through a silica column eluting with ethyl acetate/hexane (v:v, 4:1). The recovered product was converted to the HCl salt to provide 500 mg of a white solid.

Analysis for $C_{298}H_{40}N_2O_4$·HCl: Theory: C, 67.36; H, 7.99; N, 5.41; Found: C, 67.65; H, 7.94; N, 5.36.

EXAMPLE 55

Preparation of 2-[[2-(phenylmethyl)-1-oxo-3-[4-(3-hydroxyphenyl)3,4-dimethyl-1-piperidinyl]propyl]amino]-ethanoic acid phenylmethyl ester hydrochloride [X$OCH_2(CH_6H_5)$·HCl]

Acetic acid ester prepared as in Example 43 (HCl salt) (1.0 g), 3 angstrom molecular sieve (0.5 g), and benzyl alcohol (40 ml) saturated with Gaseous HCl were combined and stirred at room temperature for 72 hours. The mixture was then heated at 50° C. for 24 hours. The mixture was filtered and the solvent removed under vacuum. The residue was diluted with water and the pH was adjusted to 9.8 with triethylamine. The product was extracted into ethyl acetate which was dried over K_2CO_3. The ethyl acetate was evaporated under vacuum and the resulting residue passed through a silica column eluting with ethyl acetate/hexane (v:v, 4:1). The resulting product was converted to the HCl salt and dried to provide 300 mg of white solid.

m.p.=80°–110° C. (foam):

Analysis for $C_{32}H_{38}N_2O_4$·HCl H_2O: Theory: C, 67.53; H, 7.26; N, 4.92; Found: C, 67.51; H, 7.09; N, 4.99.

EXAMPLE 56

Preparation of 2-[[2-(phenylmethyl)-1-oxo-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]propyl]amino]-propanoic acid phenylmethyl ester hydrochloride [Z-$NH(CH_2)_2C(O)OCH_2(CH_6H_5)$·HCl]

Propanoic acid prepared as in Example 4B (1.23 g), benzyl-3-amino-propionate.p-tosylate (1.22 g), Hobt (473 mg) and TEA (0.418 ml) were combined in DMF (100 ml) and stirred ten minutes at 0° C. DCC (719 mg) was then added and the mixture allowed to warm to room temperature and the stirring was continued for three days at room temperature. The solvent was removed and the residue diluted with butanol-toluene (v:v, 3:1) and water. The pH of the aqueous layer was adjusted to 9.8 with ammonium hydroxide and the mixture extracted with butanol-toluene (3:1). The organic layer was separated and dried over K_2CO_3. The solvent was removed and resulting residue passed through a silica column eluting with ethyl acetate/hexane (v:v, 3:1). Removal of solvent provided 1.2 g of product. The product was converted to the HCl salt and dried to provide a white solid.

m.p.=70°–85° C.

Analysis for $C_{33}H_{40}N_2O_4$·HCl: Theory: C, 70.13; H, 7.31; N, 4.96; Found: C, 70.40; H, 7.27; N, 5.21.

EXAMPLE 57

Preparation of
2-[[3-[4-(3-hydroxyphenyl)3,4-dimethyl-1-piperidinyl]-1-oxo-2-(phenylmethyl)propyl]-amino]propanoic acid monohydrate Z-NH(CH_2)$_2$C(O)OH·H_2O]

The product of Example 56 (700 mg) was contacted with 5% Pd/C and Hz at 60 psi overnight. The mixture was filtered and the solvent was removed. The residue was diluted with a water/ethanol mixture. The pH was adjusted to 7.0 with 1N NaOH. This solvent was removed and the residue slurried in ethanol and filtered to remove NaCl. The solvent was removed from the filtrate and the residue passed through silica gel column eluting with ethyl acetate/ethanol (v:v, 1:1). The solvent was removed and the solid was dried to provide 366 mg of product.

m.p.=98°-100° C.

Analysis for $C_{26}H_{34}N_2O_4·H_2O$ Theory: C, 68.39; H, 7.94; N, 6.12; Found: C, 68.59; H, 8.03; N, 5.72.

EXAMPLE 58

Preparation of
[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxo-2-(phenylmethyl)propyl]-amino]propanoic acid ethyl ester monohydrochloride
[Z-NH(CH_2)$_2$C(O)OCH_2CH_3·HCl]

Propanoic acid prepared as in Example 4B (1.65 g), β-alanine ethyl ester.HCl (691 mg), TEA (454 mg), Hobt (608 mg) and dried DMF (75 ml) were combined followed by DCC (928 mg) and stirred 64 hours at room temperature under nitrogen. The mixture was evaporated to dryness and the residue partitioned between ethyl acetate and water. The layers were separated with the organic layer being washed with water, dried over K_2CO_3 and evaporated to dryness to provide 2.0 g of material. This material was passed through a silica column eluting with a gradient of hexane/ethyl acetate (v:v, 1:1) to ethyl acetate providing 1.26 g of product. This product was converted to the HCl salt and dried to provide 1.3 g of white solid.

m.p.=119°-124° C.

ms (fd)=466 M+

EXAMPLE 59

Preparation of
N-(methyl)-3-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(phenylmethyl)-1-oxopropyl]amino]-propanamide monohydrochloride
[Z-NH(CH_2)$_2$C(O)NHCH_3·HCl]

Propionic acid ethyl ester prepared as in Example 58 (450 mg), methylamine (15 ml, 40% in water), and methanol (10 ml) were combined and stirred at room temperature for three hours. The reaction was evaporated to dryness. The residue was partitioned between butanol/toluene (v:v, 3:1) and water. The H_2O layer was adjusted to a pH of 9.8 with 1N NaOH and the layers separated. The organic layer was washed one time with water, dried over K_2CO_3, and evaporated to provide 440 mg of material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1) providing 344 mg of product.

ms (fd)=451 M+, 452 M++1

The product was converted to the HCl salt and dried to provide 260 mg of white solid.

m.p=95°-99° C. (foam):

Analysis for $C_{27}H_{37}N_3O_3$·HCl: Theory: C, 66.45; H, 7.85; N, 8.61; Found: C, 66.75; H, 7.99; N, 8.46.

EXAMPLE 60

Preparation of
N-(ethyl)-3-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(phenylmethyl)-1-oxopropyl]amino]-propanamide monohydrochloride
[Z-NH(CH_2)$_2$C(O)NHCH_2CH_3·HCl]

The procedure of Example 59 was followed using propionic acid ethyl ester prepared as in Example 58 (400 mg) and ethylamine (20 ml, 70 wt. % in water) with stirring for 3.5 days. The 380 mg of material recovered was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 1:1) providing 360 mg of product.

ms (fd)=465 M+, 466 M++1

This material was converted to the HCl salt and dried to provide 300 mg of white solid.

m.p.=86°-90° C.

Analysis for $C_{28}H_{39}N_3O_3$·HCl: Theory C, 66.98; H, 8.03; N, 8.37; Found: C, 66.69; H, 7.89; N, 8.28.

EXAMPLE 61

Preparation of
4-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-1-oxo-2-(phenylmethyl)propyl]-amino]butanoic acid ethyl ester monohydrochloride monohydrate
[Z-NH(CH_2)$_3$C(O)OCH_2CH_3·HCl·H_2O]

Propanoic acid prepared as in Example 4B (HCl salt) (530 mg), TEA (0.452 ml), ethyl-4-aminobutyrate·HCl (297 mg), Hobt (218 mg), DMF (60 ml), were combined followed by the addition of DCC (333 mg). The mixture was stirred at room temperature for three days, filtered and the solvent removed. The residue was diluted with a water/ethyl acetate mixture and the water layer adjusted to a pH of 9.8 with TEA. The mixture was extracted with ethyl acetate and the organic layer separated and dried over K_2CO_3. The solvent was removed to yield 1.0 gram of material. This was passed through a silica gel column eluting with ethyl acetate. The solvent was removed to yield 300 mg of product. This product was converted to the HCl salt to give 370 mg of white solid.

m.p.=65°-70° C.

Analysis for $C_{26}H_{41}N_2O_4·H_2O$·HCl: Theory: C, 65.09; H, 8.09; N, 5.23; Found: C, 65.26; H, 7.74; N, 5.53.

EXAMPLE 62

Preparation of
N-(methyl)-4-[[3-]4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(phenylmethyl)-1-oxopropyl]amino]-butanamide monohydrochloride monohydrate
[Z-NH(CH_2)$_3$C(O)NHCH_3·HCl·H_2O]

The procedure of Example 59 was followed with the product from the procedure of Example 61 (HCl salt) (400 mg), methylamine (10 ml, 40 wt. % in water) and methanol (10 ml) with a three hour reaction time. 400 mg of material were recovered and subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1). After evaporation of solvent, 280 mg of product were recovered.

ms (fd)=465 M+, 466 M++1

This material was converted to the HCl salt and dried to provide 260 mg of white solid.

m.p.=90°-93° C. (foam):

Analysis for $C_{28}H_{39}N_3O_3 \cdot HCl\ H_2O$: Theory: C, 64.78; H, 7.96; N, 8.09; Found: C, 64.38; H, 7.73; N, 7.89.

EXAMPLE 63

Preparation of 4-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(phenylmethyl)-1-oxopropyl]-amino]butanamide monohydrochloride -$NH(CH_2)_3C(O)-NH_2 \cdot HCl$]

The procedure of Example 59 was followed with the product from the procedure of Example 61 (HCl salt) (400 mg), ammonium hydroxide (10 ml, 28% in water) and methanol (5 ml) with the reaction mixture heated at 40° C. for two days. The 400 mg of material recovered was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1) which provided 250 mg of product.

ms (fd)=451 M+

This product was converted to the HCl salt and dried to provide 200 mg of tan solid.

m.p.=101°-107° C.

Analysis for $C_{27}H_{37}N_3O_3 \cdot HCl$: Theory: C, 66.4; H, 7.85; N, 8.61; Found: C, 66.04; H, 7.86; N, 8.46.

EXAMPLE 64

Preparation of N-(ethyl)-4-[[3-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(phenylmethyl)-1-oxopropyl]amino]-butanamide monohydrochloride [Z-$NH(CH_2)_3C(O)NHCH_2CH_3 \cdot HCl$]

The procedure of Example 59 was followed with the product from the procedure of Example 61 (HCl salt) (450 mg) and ethylamine (15 ml, 70% in water) with stirring for 3.5 days to provide 440 mg of material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 1:1) providing 230 mg of product.

ms (fd)=479 M+, 480 M++1

This product was converted to the HCl salt and dried to provide 210 mg of white solid.

m.p.=105°-110° C.

Analysis for $C_{29}H_{41}N_3O_3 \cdot HCl$: Theory: C, 67.49; H, 8.20; N, 8.14; Found: C, 67.62; H, 8.28; N, 8.07.

EXAMPLE 65

Preparation of [[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-methyl]-1-oxo-3-phenylpropyl]-methylamino]acetic acid ethyl ester monohydrochloride. Z-$N(CH_3)CH_2C(O)OCH_2CH_3 \cdot HCl$]

Product from the procedure of Example 4B (1.5 g), sarcosine ethyl ester.HCl (614 mg), TEA (405 mg), Hobt (540 mg) were combined in dry DMF (75 ml) and then DCC (824 mg) was introduced. The mixture was stirred at room temperature under nitrogen for three days. The mixture was filtered and evaporated to dryness. Resulting residue was dissolved in ethyl acetate, washed one time with water and dried over K_2CO_3. Evaporation of the solvent yielded 1.72 g of material. This material was subjected to column chromatography eluting with a gradient of hexane/ethyl acetate (1:1) to ethyl acetate. The solvent was removed to yield 910 mg of product. A portion of this product was converted to the HCl salt to produce a white solid.

ms (fd)=466 M+

m.p.=91°-95° C.

Analysis for $C_{28}H_{38}N_2O_4 \cdot HCl$: Theory: C, 66.85; H, 7.81; N, 5.57; Found: C, 66.63; H, 7.81; N, 5.62.

EXAMPLE 66

Preparation of [[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-methyl]-1-oxo-3-phenylpropyl]-methylamino]acetic acid monohydrate [Z-$N(CH_3)CH_2C(O)OH \cdot H_2O$]

Product from the procedure of Example 65 (660 mg) and lithium hydroxide (176 mg) were combined in a mixture of THF/H_2O/methanol (20 ml, 3:1:1) and stirred at room temperature for three hours. The reaction mixture was poured into 10% HCl in water and extracted with a butanol-toluene (3:1) solution. The organic layer was washed with water and dried over K_2CO_3. Evaporation of the solvent under vacuum yielded 700 mg of a semi-solid material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 1:1). The solvent was removed to yield 350 mg of solid material.

ms (fd)=438 M+, 439 M++1

This material was recrystallized from ethyl acetate to yield 220 mg of crystalline product.

m.p. of 134°-136° C.

Analysis for $C_{26}H_{34}N_2O_4 \cdot H_2O$: Theory: C, 68.39; H, 7.95; N, 6.39; Found: C, 68.25; H, 7.76; N, 6.11.

EXAMPLE 67

Preparation of [[2-[2-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-3-phenyl-1-oxopropyl]-amino]acetyl]amino]acetic acid ethyl ester monohydrochloride [Z-$NHCH_2C(O)NHCH_2C(O)OCH_2CH_3 \cdot HCl$]

The procedure of Example 65 was used with the product from the procedure of Example 48 [Z-OH] (1.5 g), Glycyl Glycine ethyl ester·HCl (786 mg), TEA (405 mg), Hobt (540 mg), dry DMF (75 ml) and DCC (824 mg). 1.36 g of material were recovered. This material was passed over a silica column eluting with ethyl acetate to provide 790 mg of product.

ms (fd)=509 M+

A portion of the material was converted to the HCl salt and dried to yield a white solid.

m.p.=105°-110° C.

Analysis for $C_{29}H_{39}N_3O_5 \cdot HCl$: Theory: C, 63.78; H, 7.38; N, 7.69; Found: C, 63 77; H, 7.47; N, 7.75.

EXAMPLE 68

Preparation of N-(carboxylmethyl-)-2-[[3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-(phenylmethyl)-1-oxopropyl-]amino]acetamide monohydrate[Z-$NHCH_2C(O)NHCH_2C(O)OH \cdot H_2O$]

Procedure of Example 66 was followed with the ester product from Example 67 (500 mg) and lithium hydroxide (126 mg) in THF/H_2O/methanol (20 ml, 12:4:4). The mixture was stirred four hours at room temperature and 400 mg of material recovered. This material was passed over a silica column eluting with a gradient of ethyl acetate/methanol (v:v, 9:1) to methanol to provide 210 mg of solid product.

m.p.=124.5°-127° C.

ms (fd)=482 M+

Analysis for $C_{27}H_{35}N_3O_5 \cdot H_2O$: Theory: C, 64.91; H, 7.47; N, 8.41; Found: C, 64.64; H, 7.28; N, 8.62.

EXAMPLE 69

Preparation of N-[2-(dimethylamino)ethyl]-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidine]-2-phenylmethylpropanamide dihydrochloride [Z-NH(CH_2)$_2$-N(CH_3)$_2$·2HCl]

Procedure of Example 65 was followed with product from the procedure of Example 4B (1 g), Dimethylethylene Diamine (238 mg), Hobt (364 mg), dry DMF (50 ml) and DCC (556 mg). After evaporating the solvent, the residue was dissolved in a butanol/toluene mixture (3:1) which was washed one time with water and dried over K_2CO_3. The solvent was evaporated to provide 1.94 g of crude material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate/methanol (v:v, 9:1) to ethyl acetate/methanol (v:v, 1:1). Removal of solvent provided 700 mg of product.

ms (fd)=437 M+, 438 M$^+$+1

This product was coverted to the di-hydrochloride salt yielding a white solid.

m.p.=89°–93° C.

Analysis for $C_{27}H_{39}N_3O_2$·2HCl: Theory: C, 63.52; H, 8.10; N, 8.23; Found: C, 63.32; H, 8.20; N, 8.42.

EXAMPLE 70

Preparation of 2-methyl amine, 4-ethyl-oxadiazole monohydrochloride

A. Sodium (9.2 g) was added to methanol (200 ml) to provide sodium methoxide. Hydroxylamine hydrochloride (26.2 g) was then added. Propionitrile (24.16 g) in methanol (50 ml) was added dropwise. The mixture was then stirred for 48 hours at room temperature. The solvent was removed and the solid was taken into ethyl ether and filtered. The ether filtrate was removed and the residue was passed through a silica column eluting with ethyl acetate to provide 13 g of N-Hydroxypropaneinidamide [$H_3CCH_2C(NHOH)NH_2$].

ms (fd)=89 M+

B. Glycine ethyl ester hydrochloride (27.92 g) was combined with a mixture of water (382 ml) and dioxane (700 ml) and 1N NaOH (380 ml). To this mixture was added di-tert-butyldicarbonate (94 g) dropwise while maintaining the reaction mixture at 0°–5° C. The mixture was then stirred overnight at room temperature. Dioxane was removed under vacuum and the remaining mixture extracted with ethyl acetate. The organic layer was recovered and dried over K_2CO_3. The solvent was removed to yield 40 g of material. Bulb to bulb distillation at 145° C. under 0.05 mm Hg provided 20 g of di-tert-butyldicarbonate-glycine ethyl ester as a colorless oil. [$(CH_3)_3COC(O)NHCH_2C(O)OCH_2CH_3$]

Analysis: ($C_9H_{17}NO_4$) Theory: C, 53.19; H, 8.43; N, 6.89; Found: C, 53.05; H, 8.12; N, 6.80.

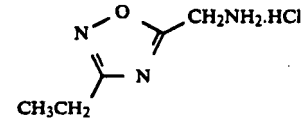
ms (fd)=203 M+

C. To ethanol (20 ml) under a nitrogen blanket was added sodium (436 mg) followed by powdered molecular sieve (4 angstrom) (20 mg) and the oxime from Example 70A above (1.3 g). To this mixture was added the product from Example 70B. above (3.26 g) dropwise as a solution in ethanol (20 ml). The mixture was then refluxed for 16 hours, filtered over celite and the solvent removed The resulting oil was partitioned between methylene chloride and water. The organic layer was dried over sodium sulfate. The solvent was removed under vacuum to provide a yellow oil (3.0 g). This material was passed through a silica column eluting with ethyl acetate to provide 1.0 g of oxadiazole.

Analysis: $C_{10}H_{17}N_3O_3$ Theory: C, 53.32; H, 6.71; N, 18.66; Found: C, 52.12; H, 7.59; N, 18.99.

ms (fd)=228 M$^+$+1

To 900 mg of the oxadiazole were added dioxane (60 ml) and 1N HCl (70 ml). The mixture was allowed to stir for two hours at room temperature. Water was removed under vacuum. Acetonitrile (100 ml) was added and solvent removed under vacuum. The product was recrystallized from acetonitrile to afford 430 mg of solid product.



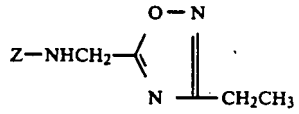
m.p.=158°–161° C.

ms (fd)=127 M+

Analysis for $C_5H_9N_3O$·HCl Theory: C, 36.71; H, 6.16; N, 25.68; Found C, 35.83; H, 5.84; N, 24.86.

EXAMPLE 71

Preparation of 3-[4-(3-hydroxyphenyl)-3,4-dimethyl1-piperidinyl]-2-(phenylmethyl)-N-[(3-ethyl-1,2,4-oxadiazol-5-yl)methyl]propanamide



Carboxylic acid product from the procedure of Example 4B (918 mg), amine.HCl product from Example 70 C. (400 mg), Hobt (338 mg), TEA (253 mg), dry DMF (75 ml) and DCC (515 mg) were combined and stirred at room temperature under nitrogen for three days. The mixture was then evaporated under vacuum to dryness. The residue dissolved in ethyl acetate, washed two times with water and the solution dried over K_2CO_3. The liquid was evaporated under vacuum to provide 1.71 g of material. This material was subjected to column chromatography eluting with a gradient of hexane/ethyl acetate (1:1) to ethyl acetate to afford 710 mg of a viscous oil. This product was converted to HCl salt.

ms (fd)=476 M+, 477 M$^+$+1

m.p.=103°–107° C.

Analysis for $C_{28}H_{36}N_4O_3$·HCl: Theory: C, 65.55; H, 7.27; N, 10.92; Found C, 65.26; H, 7.15; N, 10.70.

EXAMPLE 72

Preparation of 2-(2-Aminoacetyl)(amino)-N-(Phenylmethyl)-acetamide [$H_2NCH_2C(O)NHCH_2C(O)NHCH_2C(O)NHCH_2$-($C_6H_5$]

A. The procedure of Example 65 was followed with t-butoxycarbon-yl glycine (3 g), benzylamine (1.82 g), Hobt (2.30 g) and DCC (3.50 g) to provide 5.16 g of solid product. t-butoxycarbonyl-2-Amino-N-(Phenylmethyl)-acetamide[$(CH_3)_3COC(O)$-NH-CH_2-C(O)-NH-CH_2-C_6H_5]

B. The product from 72A above (5.16 g) was combined with 6N HCl (200 ml) and stirred overnight at room temperature. The mixture was then diluted with water (200 ml) and the pH adjusted to 11.5 with NaOH (50%) and ice. This mixture was extracted with a mixture of butanol and toluene (3:1). The organic layer was backwashed one time with water dried over K_2CO_3 and evaporated under vacuum to provide 2.1 g of solid material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate/-methanol (v:v, 9:1) to ethyl acetate/methanol (v:v, 1:1). 1.60 g of product was recovered. 2-Amino-N-(Phenylmethyl)-Acetamide[$H_2NCH_2C(O)NHCH_2C_6H_5$].

ms (fd)=164 M+

C. Product from 72B above (1.5 g), t-butoxycarbonyl glycine (1.59 g), Hobt (1.85 g) and dry DMF (75 ml) were combined followed by DCC (1.22 g). The mixture was stirred under nitrogen at room temperature for three days. The resulting mixture was filtered and evaporated to dryness. The residue was dissolved in ethyl acetate, filtered and dried over K_2CO_3. The solvent was evaporated to provide 8.14 g of butoxycarbonyl-2-(2-amineacetyl)-(amino)-N-(Phenylmethyl)-acetamide[$(CH_3)COC(O)NHCH_2C(O)NHCH_2$.$C(O)NHCH_2C_6H_5$].

D. Product from 72C above (8.14 g) was combined with 6N HCl (150 ml) using the procedure of Example 72B to provide 2 g of product. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (1:1) providing 700 mg of crystalline product. [$H_2NCH_2C(O)NHCH_2C(O)NHCH_2C_6H_5$].

m.p.=113°-116° C.

ms (fd)=201 M+

EXAMPLE 73

Preparation of X-NH-$CH_2C(O)$-NH-$CH_2C_6H_5$

Carboxylic acid product of the procedure of Example 4B (886 mg), amine product from Example 72 D (700 mg), Hobt (405 mg) and dry DMF (50 ml) were combined and then DCC (618 mg) was added. This mixture was stirred 72 hours at room temperature, filtered and evaporated under vacuum to provide 2.0 g of material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1) providing 860 mg of product.

ms (fd)=570 M+, 571 M+ +1

This product was converted to the HCl salt.

m.p.=119°-122° C.

Analysis $C_{34}H_{42}N_4O_4$·HCl: Theory: C, 67.26; H, 7.14; N, 9.23; Found: C, 67.48; H, 7.07; N, 9.12.

EXAMPLE 74

Preparation of $NH_2CH_2C(O)N(CH_3)CH_2C(O)OCH_2CH_3$·HCl

A. t-butoxycarbonyl glycine (3 g), Sarcosine Ethyl Ester·HCl (2.61 g), TEA (1.72 g), Hobt (2.30 g) and DMF (125 ml) were combined and DCC (3.5 g) was added. This mixture was stirred for 72 hours at room temperature, filtered and evaporated to dryness under vacuum. 8.1 g of material was recovered. This was passed through a silica column eluting with a gradient of ethyl acetate to ethyl acetate/methanol (1:1) providing 2.9 g. of product $(CH_3)_3OC(O)NHCH_2$.$C(O)N(CH_3)CH_2C(O)OCH_2CH_3$].

ms (fd)=274 M+, 275 M+ +1

B. The product from Example 74A (2.90 g), 1N HCl (50 ml), and ethyl acetate (10 ml) were combined and stirred at room temperature for three hours. The mixture was evaporated to dryness. The residue triturated in acetonitrile and ethyl ether The solid which formed was filtered to provide 900 mg of the HCl salt. [$H_2NCH_2C(O)N(CH_3)CH_2C(O)OCH_2CH_3$·HCl].

ms (fd)=174 M+

EXAMPLE 75

Preparation of X-$N(CH_3)CH_2C(O)OCH_2CH_3$

Carboxylic acid product from the procedure of Example 4B (Z-OH) (1.15 g), product from Example 74B (900 mg), TEA (434 mg), Hobt (580 mg) and dry DMF (50 ml) were combined followed by the addition of DCC (886 mg). The mixture was stirred for three days at room temperature under nitrogen. The mixture was filtered and evaporated to dryness The residue was dissolved in ethyl acetate, washed one time with water, dried over K_2CO_3 and the solvent evaporated to provide 2.47 g of material. This was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 9:1) providing 1.7 g of material This was again passed through a silica column eluting with ethyl acetate to provide 150 mgs of semi-solid material.

ms (fd)=523 M+, 524 M+ +1

The material was converted to HCl salt to yield 100 mgs a white powder.

m.p.=104°-107° C.

Analysis for $C_{30}H_{41}N_3O_5$·HCl: Theory: C, 64.33; H, 7.56; N, 7.50; Found: C, 64.61; H, 7.55; N, 7.27.

EXAMPLE 76

Preparation of $H_2NCH_2C(O)NHCH_2C(O)NHCH_2CH_3$

A. t-butoxycarbonyl- glycine (3 g), ethylamine.HCl (1.39 g), TEA (1.72 g), Hobt (2.3 g) and dry DMF (100 ml) were combined and DCC (3.5 g) was added. The mixture was stirred for three days at room temperature under nitrogen, then filtered and evaporated to dryness. 6 g of material was recovered. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (1:1) providing 4.01 g of $(CH_3)_3COC(O)NHCH_2$.$C(O)NHCH_2CH_3$.

ms (fd)=202 M+

B. Product from 76A above (4 g) and 6N HCl (150 ml) were mixed and stirred overnight at room temperature. Acetonitrile was added and the solution was evaporated to dryness. The resulting solid was slurried in ethyl ether, filtered and dried to provide 1.84 g. of $H_2NCH_2C(O)NHCH_2CH_3$·HCl.

ms (fd)=102 M+

C. The product from 76B above (1.80 g), t-butoxycarbonylglycine (2.28 g), TEA (1.31 g), Hobt (1.76 g) and dry DMF (150 ml) were combined and DCC (2.68 g) was added. The mixture was stirred for three days at room temperature under nitrogen, filtered and evaporated to dryness. The residue was dissolved in ethyl acetate which was washed one time with water, dried over K_2CO_3 and evaporated to provide 2.15 g of material. This material was subjected to column chromatography eluting with a gradient of ethyl acetate/methanol (v:v, 9:1) to ethyl acetate/methanol (v:v, 1:1) providing 920 mg of $(CH_3)_3COC(O)$-$NHCH_2C(O)NHCH_2$.$C(O)NHCH_2CH_3$.

ms (fd)=259 M+

D. The product from 76C above (900 mg) and 6N HCl (40 ml) were combined as in Example 74 B to provide 700 mg of product as the HCl salt.

ms (fd)=160 M+

EXAMPLE 77

Preparation of X-NHCH$_2$C(O)NHCH$_2$C(O)NHCH$_2$CH$_3$

The procedure of Example 76A was followed with the carboxylic acid prepared from the procedure of Example 4B (Z-OH) (774 mg), amine.HCl product from Example 76 D (458 mg), TEA (293 mg), Hobt (391 mg), dry DMF (50 ml) and DCC (597 mg). 1.74 g of material was recovered. This material was subjected to column chromatography eluting with a gradient of ethyl acetate to ethyl acetate/methanol (1:1) providing 510 mg of product.

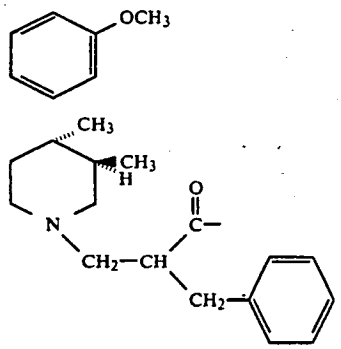
ms (fd)=508 M+, 509 M++1

This product was converted to HCl salt to provide 400 mg of solid.

m.p.=110°-115° C.

Analysis for $C_{29}H_{40}N_4O_4$·HCl: Theory: C, 63.90; H, 7.58; N, 10.28; Found: C, 64.16; H, 7.29; N, 10.06.

In Examples 78 thru 82, W is



EXAMPLE 78

Preparation of W-OCH$_2$CH$_3$

A. Trans-(+)- 1,3,4-trimethyl-4-(3-methoxyphenyl)-piperidine (3.48 g) vinyl chloroformate (2.73 ml) and proton sponge (7.13 g) were mixed in 1, 2-dichloroethane (150 ml), refluxed for 2 hours, cooled to room temperature and evaporated to dryness. The resulting residue was dissolved in ethyl ether, washed two times with cold 1N HCl, one time with water, dried over K_2CO_3, and evaporated to dryness to provide 4.51 g of the carbamate product. The carbamate was mixed with ethanol (100 ml) and ethanol/gaseous HCl (100 ml) and refluxed for 1.5 hours. The mixture was cooled to room temperature and evaporated to dryness. The residue was dissolved in 1N NaOH and ethyl ether added. The ether layer was separated, washed with water, dried over K_2CO_3 and evaporated to provide 3.0 grams of material. This was vacuum distilled in a bulb-to-bulb distillation apparatus at 220° C. and 0.1 mmHg to provide 2.86 g of trans-3,4-dimethyl-4-(3-methoxyphenyl)-piperidine.

B. The product from 78A above (2.86 g) and 3-phenyl-2-(ethoxycarbonyl)-1-propene prepared as in Example 2 (2..72 g) and methanol (50 ml) were mixed and stirred at room temperature under nitrogen for 10 days. The mixture was evaporated 2 times and rediluted with methanol on day 5 and day 9. On day 10 the mixture was evaporated to dryness to provide 5.46 g of material which was subjected to column chromatography eluting with a gradient of hexane to ethyl acetate. Removal of solvent provided 4.05 g of product.

ms (fd)=409 M+, 410 M++1

A portion of the product was converted to the HCl salt.

m.p.=61°-64° C.

Analysis for $C_{26}H_{35}NO_3$·HCl: Theory: C, 70.01; H, 8.13; N, 3.14; Found: C, 70.00; H, 8.02; N 3.17.

EXAMPLE 79

Preparation of W-OH

The method of Example 12 was followed with W-OCH$_2$CH$_3$ prepared as in Example 78B (2.03 g) and lithium hydroxide (6.29 mg) in THF/H$_2$O/methanol (63:21:21). Evaporation of the solvent yielded 1.82 grams of crystalline material as the HCl salt. This material was recrystallized from acetonitrile to provide 610 mg of crystalline product.

ms (fd)=481 M+

m.p.=196.5°-198° C.

Analysis $C_{24}H_{31}NO_3$·HCl: Theory: C, 68.77; H, 7.72; N, 3.35; Cl, 8.48; Found: C, 68.84; H, 7.79; N, 3.33; Cl 8.49.

EXAMPLE 80

Preparation of W-NHCH$_3$

W-OCH$_2$CH$_3$ prepared by the procedure of Example 78B (700 mg) and methylamine (25 ml 40% weight percent in water), were mixed and stirred at 50° C. for 4 days. The reaction mixture was evaporated to dryness and the residue was partitioned between a butanol-toluene (3:1) mixture and water. The pH of the water was adjusted to 9.8 with IN NaOH and layers were separated. The organic layer was washed one time with water and dried over K_2CO_3 and evaporated to provide 600 mg of material. This material was subjected to column chromatography eluting with a gradient of hexane/ethyl acetate (9:1) to ethyl acetate providing 140 mg of product.

ms (fd)=396 M+

This product was converted to the HCl salt and dried to provide 110 mg of solid.

m.p.=86°-90° C.

Analysis for $C_{25}H_{34}N_2O_2$·HCl: Theory: C, 69.67; H, 8.18; N, 6.50; Found: C, 69.91; H, 8.35; N, 6.33.

EXAMPLE 81

Preparation of W-NHCH$_2$C(O)OCH$_2$CH$_3$

W-OH prepared as in Example 79 (4.15 g), glycine ethyl ester.HCl (1.40 g), TEA (1.01 g), Hobt (1.35 g) and dry DMF (300 ml) were combined and DCC (2.06 g) was then added. The mixture was stirred at room temperature under nitrogen for 3 days, filtered and evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water, dried over K_2CO_3 and evaporated under vacuum to provide 5.65 g of material. This material was subjected to column chromatography eluting with a gradient of hexane/ethyl acetate (9:1) to ethyl acetate providing 3.40 g of product.

ms (fd)=466 M+

2 g of this material were converted to the HCl salt and dried to provide 2.13 g of white solid.

m.p.=122°-126° C.

Analysis for $C_{28}H_{38}N_2O_4$·HCl Theory: C, 66.85; H, 7.81; N, 5.57; Found: C, 67.11; H, 7.99; N, 5.61.

EXAMPLE 82

Preparation of W-$NHCH_2C(O)NHCH_3$

The procedure of Example 80 was followed with W-$NH{\cdot}CH_2C(O)OCH_2CH_3$ prepared as in Example 81 (600 mg) and methylamine (25 ml, 40 wt % in water) for 2 hours at room temperature. 580 mg of product was recovered. This was passed over a silica column eluting with ethyl acetate to provide 350 mg of material.

ms (fd)=451 M+

This was converted to the HCl salt and dried to provide 380 mg of a white solid.

m.p.=101°-106° C.

Analysis for $C_{27}H_{37}N_3O_3$·HCl: Theory: C, 66.44; H, 7.85; N, 8.61; Found: C, 66.25; H, 7.90; N, 8.58.

EXAMPLE 83

Preparation of W-$NHCH_2C(O)NHCH_2CH_3$

The procedure of Example 80 was followed with W-$NHCH_2C(O)OCH_2CH_3$ prepared as in Example 81 (600 mg) and ethylamine (25 ml, 70 wt % in water stirring for two hours at room temperature. 610 mg of material were recovered. This material was passed over a silica column eluting with ethyl acetate to provide 400 mg of product.

ms (fd)=465 M+

This product was converted to the HCl salt and dried to provide 425 mg of white solid.

m.p.=103°-108° C.

Analysis for $C_{28}H_{39}N_3O_3$·HCl: Theory: C, 66.98; H, 8.03; N, 8.37; Found: C, 66.71; H, 8.11; N, 8.38.

EXAMPLE 84

A Preparation of N,N-dimethyl-2-hydroxyacetamide

Methyl-2-hydroxyethanoate (10 g) and dimethylamine (100 ml, 40 weight percent in water) were mixed and stirred at room temperature for three hours. The mixture was evaporated to dryness to provide approximately 10 g of material. This material was subjected to column chromatography eluting with a gradient of hexane/ethyl acetate (V:V, 4:1) to ethyl acetate. Removal of the solvent provided 8.12 g of crystalline product.

ms (fd)=103 M+

m.p.=40°-42° C.

I.R.=1655.4 cm^{-1} (carbonyl)

Analysis for $C_4H_9NO_2$: Theory: C, 46.59; H, 8.80; N, 13.59; Found: C, 46.44; H, 8.69; N, 13.60.

B. Preparation of N-methyl-2-hydroxyacetamide

The procedure of 84A was followed using methylamine (100 ml, 40 weight percent in water) as the amine. 10.2 g of material was obtained which was slurried in toluene and evaporated to remove water. This material was passed over a silica column eluting with ethyl acetate to provide 7.13 g of solid product.

m.p.=66.5°-68° C.

ms (fd)=89 M+

Analysis for $C_3H_7NO_2$: Theory: C, 40.44; H, 7.92; N, 15.72; Found: C, 40.36; H, 7.75; N, 15.54.

C. Preparation of N-ethyl-2-hydroxyacetamide

The procedure of 84A was followed with ethylamine (100 ml, 70 weight percent in water) as the amine to provide 11.26 g of an oil. This material was passed over a silica column eluting with ethyl acetate. 7.2 g of product was recovered as white crystals.

m.p.=79°-82° C.

ms (fd)=103 M+

Analysis for $C_4H_9NO_2$: Theory: C, 46.59; H, 8.80; N, 13.58; Found: C, 46.86; H, 8.41; N, 14.00.

D. Preparation of 2-hydroxyacetamide

The procedure of 84A was followed using ammonium hydroxide (100 ml, 28% in H_2O) to provide 10.3 g of crystalline material. This material was recrystallized from ethyl acetate/ethanol (v:v, 4:1) to provide 6.0 g of white crystal product.

m.p.=111°-112.5° C.

ms (fd)=75 M+

Analysis for $C_2H_5NO_2$: Theory: C, 32.00; H, 6.71; N, 18.66; Found: C, 32.02; H, 6.49; N, 18.43.

E. Preparation of N-benzyl-2-hydroxyacetamide

The procedure of 84A was followed with methyl2-hydroxyethanoate (8 g) and benzylamine (10 ml in 30 ml H_2O). After one hour material precipitated out of solution. The mixture was stirred overnight, and the solid recovered by filtration to provide 4.12 g of white solid. The solvent was removed from the filtrate by vacuum to provide 4.71 g of material The solid and filtrate were combined and passed over a silica column eluting with a gradient of ethyl acetate to ethyl acetate/methanol (v:v, 1:1). Removal of solvent provided 8 g of white crystal product.

m.p.=101°-102° C.

ms (fd)=165 M+

I.R.=1634.88 cm^{-1} (carbonyl)

Analysis for $C_9H_{11}NO_2$: Theory: C, 65.44; H, 6.71; N, 8.48; Found: C, 65.39; H, 6.83; N, 8.62.

In Examples 85 through 95, X represents Z-$NHCH_2C(O)$- where Z is as set forth for Example 73.

EXAMPLE 85

Preparation of X-$OCH_2C(O)OCH_3$

The carboxylic acid X-OH prepared as in Example 44 (1.5 g), methyl glycolate (315 mg), Hobt (473 mg) and dry DMF (125 ml) were combined and DCC (721 mg) was then added. The mixture was stirred at room temperature under nitrogen for 24 hours. The mixture was filtered and evaporated under vacuum to dryness. The residue was dissolved in ethyl acetate which was washed once with water, dried over K_2CO_3 and evaporated under vacuum to provide 1.86 g of an orange semi-solid material. This material was subjected to column chromatography eluting with a gradient of hexane/ethyl acetate (v:v, 9:1) to ethyl acetate. Removal of the solid provided 1.41 g of an orange material which was then passed over a chromatron using 4000 micron plate and eluting with hexane/ethyl acetate (1:1) to provide 980 mg of material.

ms (fd)=497 M+

This material was converted to the HCl salt and dried to provide 770 mg of tan solid.

m.p.=98°-104° C.

Analysis for $C_{28}H_{36}N_2O_6$·HCl: Theory: C, 63.09; H, 7.00; N, 5.26; Found: C, 62.81; H, 7.08; N, 4.97.

EXAMPLE 86

Preparation of X-$O(CH_2)_4CH_3$

The carboxylic acid X-OH prepared as in Example 44 (500 mg), amyl alcohol (20 ml) and amyl alcohol satu-

rated with gaseous HCl gas (20 ml) were combined and refluxed under nitrogen for 1.5 hours. The mixture was then evaporated to dryness and the residue partitioned between ethyl acetate and water. The pH of the water layer was adjusted to 9.8 with 1N NaOH. The layers were separated and the ethyl acetate layer washed one time with water, dried over K_2CO_3 and evaporated to provide 660 mg of a viscous oil. This material was subjected to column chromatography eluting with a gradient of hexane/ethyl acetate (v:v, 9:1) to hexane/ethyl acetate (v:v, 1:1). Removal of solvent provided 400 mg of a white foam.

ms (fd)=494 M^+, 495 $M^+ + 1$

This material was converted to the HCl salt and dried to provide 300 mg of white solid.

m.p.=75°-81° C.

Analysis for $C_{30}H_{42}N_2O_4 \cdot HCl$: Theory: C, 66.71; H, 8.21; N, 5.19; Found: C, 66.44; H, 8.07; N, 5.35.

EXAMPLE 87

Preparation of X-O-$CH_2C(O)NH_2$

The procedure of Example 85 was followed with X-OH prepared as in Example 44 (500 mg), 2-hydroxyacetamide (90 mg), Hobt (162 mg), dry DMF (50 ml) and DCC (247 mg) to provide 660 mg of an orange oil. This material was passed over a silica column eluting with ethyl acetate providing 310 mg of a white foam. This material was passed over a chromatron using 2000 micron plate and eluting with ethyl acetate to provide 260 mg of product.

ms (fd)=482.4 $M^+ + 1$

This was converted to the HCl salt and dried to provide a white solid.

m.p.=111°-116° C.

Analysis for: $C_{27}H_{35}N_3O_5 \cdot HCl$: Theory: C, 62.60; H, 7.00; N, 8.11; Found: C, 62.61; H, 6.97; N, 7.71.

EXAMPLE 88

Preparation of X-$OCH_2C(O)NHCH_3$

The procedure of Example 85 was followed with X-OH prepared as in Example 44 (500 mg), N-methyl-2-hydroxyacetamide (107 mg), Hobt (162 mg), DMF (500 ml), and DCC (247 mg) to provide 890 mg of an oil. This material was passed over a silica column eluting with ethyl acetate with 400 mg of material recovered. This was passed over a chromatron using 2000 micron plate and eluting with ethyl acetate to provide 260 mg of a white solid.

ms (fd)=497 $M^+ + 1$

This material was converted to the HCl salt and dried to provide 2I8 m9 of a tan solid.

m.p.=114°-118° C.

Analysis for $C_{28}H_{37}N_3O_5 \cdot HCl$: Theory: C, 63.21; H, 7.20; N, 7.90; Found C, 62.90; H, 7.15; N, 7.50.

EXAMPLE 89

Preparation of X-$OCH_2C(O)NHCH_2CH_3$

The procedure of Example 85 was followed with X-OH prepared as in Example 44 (530 mg), N-ethyl-2-hydroxyacetamide (134 mg), Hobt (176 mg), dry DMF (50 ml), and DCC (268 mg) to provide 810 mg of a viscus oil. This was passed over a silica column eluting with ethyl acetate with 400 mg of a white foam recovered. This was passed over a chromatron with a 2000 micron plate eluting with ethyl aceate to provide 300 mg of product.

ms (fd)=510 $M^+ + 1$

This material was converted to the HCl salt and dried at 60° C. to provide a white solid.

m.p.=109°-113° C.

Analysis for $C_{29}H_{39}N_3O_5 \cdot HCl$: Theory: C, 63.78; H, 7.38; N, 7.69; Found: C, 63.38; H, 7.32; N, 7.47.

EXAMPLE 90

Preparation of X-$OCH_2C(O)N(CH_3)_2$

The procedure of Example 85 was followed with X-OH prepared as in Example 44 (500 mg), N,N-dimethyl-2-hydroxyacetamide (124 mg), Hobt (162 mg), dry DMF (50 ml), and DCC (247 mg) to provide 615 mg of an orange semi-solid materia. This was passed over a silica column eluting with ethyl acetate to provide 260 mg of an orange foam. This was passed over a chromatron with a 2000 micro plate eluting with ethyl acetate to provide 230 mg of a white foam.

ms (fd)=509 M^+, 510 $M^+ + 1$

This material was converted to the HCl salt and dried at 60° C. to yield 220 mgs of white solid.

m.p.=124°-130° C.

Analysis for $C_{29}H_{39}N_3O_5 \cdot HCl \cdot \frac{1}{2}H_2O$: Theory: C, 62.74; H, 7.38; N, 7.57; Found: C, 62.78; H, 7.53; N, 7.69.

EXAMPLE 91

Preparation of X-$NHCH_2(C_6H_{11})$

The procedure of Example 85 was followed with X-OH prepared as in Example 44 (500 mg), N-cyclohexylmethylene-2-hydroxyacetamide (205 mg), Hobt (162 mg), dry DMF (40 ml), and DCC (247 mg) to provide 715 mg of pale orange foam. This material was passed over a silica column eluting with ethyl acetate to provide 600 mg of material which was then passed over a chromatron using a 2000 micron plate eluting with ethyl acetate to provide 170 mg of product.

ms (fd)=519 M^+, 520 $M^+ + 1$

This material was converted to HCl salt and dried at 60° C. for two hours to provide a white solid.

m.p.=136°-140° C.

Analysis for $C_{32}H_{45}N_3O_3 \cdot HCl$: Theory: C, 69.11; H, 8.34; N, 7.56; Found C, 68.83; H, 8.38; N, 7.81.

EXAMPLE 92

Preparation of X-O-(4-methoxycyclohexyl)--hydrochloride.

X-OH prepared as in Example 44 (424 mg), K_2CO_3 (1.83 g), CIS-4-methoxycylohexyl-p-toluensulfonate (1.52 g) were combined in dry DMF (70 ml) and the mixture heated under nitrogen for 20h at reflux. The mixture was cooled, filtered, and evaporated under vacuum to yield 640 mgs. This material was subjected to column chromatography eluting with a gradient of hexane/ethyl acetate (v:v, 1:1) to ethyl acetate. Removal of the solvent provided 370 mg of a viscous oil.

ms (fd)=537 $M^+ + 1$ This material was converted to the HCl salt and dried at 60° C. to provide 300 mg of a white solid.

m.p.=116°-119° C.

Analysis for $C_{32}H_{44}N_2O_5 \cdot HCl$: Theory: C, 67.06; H, 7.91; N, 4.89; Found: C, 66.80; H, 7.82; N, 4.87.

EXAMPLE 93

Preparation of X-$OCH_2C(O)NHCH_2(C_6H_5)$·hydrochloride·monohydrate

X-OH prepared as in Example 44 (500 mg), N-benzyl-2-hydroxyacetamide (198 mg), Hobt (162 mg), dry DMF (40 ml) and DCC (247 mg) were combined as in Example 85 to provide 910 mg of a tan oil. This material was passed over a silica column eluting with ethyl acetate with 415 mg of an orange foam recovered. This material was passed over a chromatron using a 2000 micron plate and eluting with ethyl acetate to provide 160 mg of material.

ms (fd)=571 M^+, 572 $M^+ + 1$

This material was converted to HCl salt and dried at 60° to yield a white solid.

m.p.=115°–120° C.

Analysis for $C_{34}H_{41}N_3O_5$·HCl H_2O: Theory: C, 65.21; H, 7.0B; N, 6.71; Found: C, 65.23; H, 7.29; N, 6.71.

EXAMPLE 94

Preparation of X-$OCH(CH_3)OC(O)CH_3$·hydrochloride

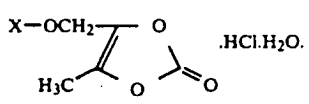
XOH prepared as in Example 44 (463 mg) and K_2CO_3 (1.83 g) were heated at 70° C. for ten minutes. The mixture was then cooled to room temperature and 1-bromoethylacetate (894 mg) in DMF (20 ml) was added dropwise at room temperature. After stirring one hour at room temperature, the solution was filtered and evaporated. The residue was partitioned between ethyl acetate and water with the water layer pH adjusted to 9.8 with 1N N_3OH. The layers were separated and the ethyl acetate layer washed one time with water, dried over K_2CO_3 and evaporated to provide 620 mg of a dark oil. This material was passed over a silica column eluting with a gradient of hexane/ethyl acetate (v:v, 1:1) to ethyl acetate. Removal of solvent provided 330 mg of a dark oil which was placed over the chromatron using a 2 mm plate and eluting with a gradient of hexane/ethyl acetate (v:v, 1:1) to ethyl acetate. The resulting solution was stirred over decolorizing charcoal and the solvent removed to provide 200 mg of a tan oil having a mass spec of 511 ($M^+ + 1$). This product was converted to HCl salt and dried at 60° C. to provide 190 mg of a tan solid.

m.p.=94°–98° C. (with decomposition)

Analysis for $C_{29}H_{38}N_2O_6$·HCl: Theory: C, 63.67; H, 7.19; N, 5.12 ; Found: C, 63.65; H, 7.32; N, 5.15.

EXAMPLE 95

Preparation of



XOH prepared as in Example 44 (636 mg) and K_2CO_3 (1.89 g) were combined and cooled to 0° C. under a nitrogen atmosphere. 4',Bromomethyl-4,5-methyl-1,3-dioxol-2-one (1.07 g) in dry methylene chloride (20 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred for one hour. The mixture was filtered and evaporated to dryness to provide 1.0 g of a dark oil. This was subjected to column chromatography eluting with a gradient of hexane/ethyl acetate (1:1) to ethyl acetate/methanol (v:v, 9:1). The removal of solvent provided 300 mg of a tan oil.

ms (fd)=537 $M^+ + 1$

A portion of this product was converted to HCl salt and dried at 60° C. to provide a white solid.

m.p.=72°–75° C.

Analysis for $C_{30}H_{36}N_2O_7$·HCl·H_2O: Theory: C, 60.95; H, 6.65; N, 4.74; Found: C, 60.84; H, 6.47; N, 4.82.

EXAMPLE 96

Preparation of sec-butyl-2-aminoaceate·para-tosylate

Glycine (7.51 g), paratoluenesulfonic acid (20.92 g), isobutyanol (20 ml) and toluene (200 ml) were combined and refluxed for five hours with a Dean Stark trap. The reaction mixture was cooled and evaporated to dryness to provide 28.11 g of crystalline product. The crystalline product was recrystallized from hexane/ethyl acetate (v:v, 4:1) to provide 27.12 g of white crystals.

m.p.=73°–74° C.

ms (fd)=132 (free base)=M+

I.R.=1738.9 cm^{-1} (carbonyl)

Analysis for $C_6H_{13}N_2O$·p-tosylate Theory: C, 51.47; H, 6.98; N, 4.62; Found: C, 51.56; H, 6.96; N, 4.59.

EXAMPLE 97

Preparation of (+)(3R,4R)-trans-[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl-]amino]acetic acid monohydrate [(+)X-OH·H_2O of Example 85].

A. Preparation of (+)-trans-(3R,4R)-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-phenylmethyl-propanoic acid, ethyl ester.

The procedure of Example 4A was followed with (+)-trans-(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-piperidine (4.4 g, 20 mmole) and 2-ethoxycarbonyl-3-phenylpropene (4.5 g) in methanol (225 ml). The reactants were stirred at room temperature under nitrogen for ten days with the reaction mixture then evaporated to dryness to provide 8.8 g of a viscous oil. This material was passed through a Prep-500 liquid chromatography eluting with a gradient of hexane to 10% ethyl acetate/hexane. 8.0 g of a white foam was recovered.

ms (fd)=395 M+

B. Preparation of (+)-trans-(3R,4R)-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl-2-phenylmethyl propanoic acid[(+)-Z-OH]

The product from 97A above (6 g, 15 mmole) and lithium hydroxide (1.89 g) were combined in a mixture of THF/methanol/water (192 ml/64 ml/64 ml) and stirred at room temperature for three hours. The mixture was then poured into 1N HCl and stirred for five minutes. The aqueous solution was then adjusted to a pH of 9.8 with triethylamine and extracted with n-butanol/tolune (3:1). The organic layer was dried over $MgSO_4$ and evaporated to provide 7.14 g of a white foam. This material was subjected to column chromatography eluting with a gradient of ethyl acetate/methanol (9:1) to ethyl acetate/methanol (1:1). Removal of solvent provided 3.98 g of a white powder.

ms (fd)=367 M^+, 368 $M^+ + 1$

C. Preparation of (+)X-$OCH_2CH(CH_3)_2$

The carboxylic acid product (+)Z-OH from 97B above (2.45 g, 6.7 mmole), the amine from Example 96 (1.82 g), triethylamine (604 mg), Hobt (806 mg), DCC (1.23 g) were combined in dry DMF (180 ml) and stirred at room temperature under nitrogen for 72 hours. The mixture was then filtered and evaporated to dryness. The residue was partitioned between ethyl acetate and water. The pH of the water layer was adjusted to 9.8 with 1N N_3OH and the layers were separated. The organic layer was dried over K_2CO_3 and then evaporated to provide 3.21 g of an orange foam. This material was passed over a silica column eluting with a gradient of hexane/ethyl acetate (9:1) to ethyl acetate. The removal of solvent provided 2.31 g of a white foam.

ms (fd)=481 M+

D. Separation of diastereomers

4.36 g of an isomeric mix prepared as in Example 97C above was passed over a Prep-500 liquid chromatograph using a gradient of hexane/triethylamine (99:1) to hexane/ethyl acetate/triethylamine (75:24:1). An 8 liter forerun was discarded and 300 ml fractions were then collected.

Fractions 38–45 contained 99% of a first peak by HPLC. Removal of solvent provided 580 mg of a white foam (Diastereomer A)[(+)-(3R,4R)-X-$OCH_2CH(CH_3)_2$. ms (fd)=481 M+

$[\alpha]_{365}=+172.65°$

Analysis for $C_{29}H_{40}N_2O_4$: Theory: C, 72.47; H, 8.39; N, 5.83; Found: C, 72.49; H, 8.59; N, 5.63.

This was converted to the HCl salt.

m.p.=91°–95° C.

Analysis for: Theory: C, 67.36; H, 7.99; N, 5.42; Found: C, 67.06; H, 7.98; N, 5.30.

Fractions 57–67 were analyzed to contain 85% of a second peak by HPLC. Removal of solvent provided 490 mg of a solid material. Recrystallization from isopropyl ether provided 410 mg of crystalline product (diastereomer B).

m.p.=136°–136.5° C.

ms (fd)=481 M+

$[\alpha]_{365}=+153.03°$

Analysis for: $C_{29}H_{40}N_2O_4$: Theory: C, 72.47; H, 8.39; N, 5.83; Found: C, 72.42; H, 8.26; N, 6.04.

E. Formation of Title Compound [(+)X-OH]

Diastereomer A prepared as in Example 97D above (300 mg), dioxane (15 ml) and 6N HCl (15 ml) were combined and refluxed for six hours. The mixture was cooled to room temperature and evaporated to dryness. The resulting solid was partitioned between water and butanol/toluene (3:1). The water layer was adjusted to a pH of 9.8 using triethylamine. The layers were separated and the organic layer dried over $MgSO_4$ and evaporated to dryness. The solid material was passed over a silica column eluting with a gradient of ethyl acetate/methanol (9:1) to methanol. Evaporation of solvent yielded 126 mgs of a white solid.

m.p.=135°–138° C.

ms (fd)'424 M+, 425 M++1

Analysis for $C_{25}H_{32}N_2O_4 \cdot H_2O$: Theory: C, 67.87; H, 7.74; N, 6.32; Found : C, 67.49; H, 7.45; N, 5.97.

EXAMPLE 98

Preparation of (—)-(3S,4S)-trans-[[2-[[4-(3-hydroxyphenyl)-3,4-dimethyl)-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl-]amino]acetic acid [(—)X-OH of Example 85]

A. Preparation of (—)-trans-(3S,4S)-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-phenylmethyl-propanoic acid ethyl ester.

The procedure of Example 97A was followed using (—)-trans (3S,4S)-4-(3-hydroxyphenyl)-3,4-dimethyl-piperidine (10 g, 48 mmole) and 2-ethoxycarbonyl-3-phenylpropene (10.2 g) in methanol (500 ml). 18.31 g of a tan viscus oil was recovered. This was passed over a PREP-500 liquid chromatograph eluting with a gradient of hexane to 10% ethyl acetate/hexane to providing 17.40 g of a white foam.

ms (fd)=395 M+

B. Preparation of (—)-(3S,4S)-3-[4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-2-phenylmethyl-propanoic acid.

The procedure of Example 97B was followed with the product from Example 97A (12.5 g, 32 mmole), lithium hydroxide (3.98 g) in THF/methanol/water (400 ml/130 ml/130 ml). 10.75 g of a tan foam was recovered. This was subjected to column chromatography eluting with a gradient of ethyl acetate/methanol (9:1) to ethyl acetate/methanol (1:1). Removal of the solvent provided 8.97 g of a white powder.

ms (fd)=368 M++1

C. Preparation of (—)-X-OCH_2-$CH(CH_3)_2$

The procedure of Example 97C was followed with the product from Example 98B (5.12 g, 14 mmole), amine from Example 96 (4.54 g), triethylamine (1.5 g), Hobt (2.0 g) DCC (3.04 g) in dry DMF (400 ml). 7.81 g of an orange foam was recovered. This was passed over a silica column eluting with a gradient of hexane/ethyl acetate (9:1) to hexane/ethyl acetate (1:1). Removal of the solvent provided 5.5 g of a white foam.

ms (fd)=481 M+

D. Separation of Diastereomers

The procedure of Example 97D was followed using 4.20 g of the (—)-isomeric mix of Example 98C.

Fractions 33–40 showed 98% of a first peak by HPLC. Removal of solvent provided 435 mg of a white foam (diastereomer A).

ms (fd)=481 M+

$[\alpha]_{365}=-172.11°$

Analysis for $C_{29}H_{40}N_2O_4$: Theory: C, 72.47; H, 8.39; N, 5.83; Found C, 72.31; H, 8.51; N, 5.66.

Fractions 54–63 showed 88% of a second peak by HPLC. Removal of solid provided 510 mg of material. This was recrystallized from isopropyl ether to provide 460 mg of a crystalline product. HPLC showed 99% of this second peak (diastereomer B).

ms (fd)=481 M+

$[\alpha]_{365}=-153.95°$

Analysis for $C_{29}H_{40}N_2O_4$: Theory: C, 72.47; H, 8.39; N, 5.83; Found C, 72.67; H, 8.35; N, 5.88.

E. Preparation of (—)X-OH

The procedure of Example 97E was followed with Diastereomer B from Example 98D (200 mg), dioxane (10 ml) and 6N HCl (10 ml) to provide 210 mg of material. This was passed over a silica column eluting with a

gradient of ethyl acetate/methanol (9:1) to methanol Removal of the solvent provided 101 mg of product.

m.p. = 130°–133° C.

ms (fd) = 421 $M^+ + 1$

$[\alpha]365$ (−115.16°)

Analysis for $C_{25}H_{32}N_2O_4 \cdot H_2O$ Theory C 67.87 H 7.7N 6.32; Found C 68.07 H 7.34 N 6.15.

The instant compounds are useful in blocking peripherial opioid receptors and preventing peripherally opiate induced side effects These side effects induced by the administration of an opiate such as morphine to a mammal can include constipation, nausea, and vomiting. These compounds can also be useful in the treatment of irritable bowel syndrome and idiopathic constipation. While not wishing to be bound by the theory, it is believed that the instant compounds act as opioid antagonists and bind to peripherial opioid receptors outside of the brain. The compounds do not substantially pass through the blood-brain barrier and therefore do not mitigate the opioid's effect on central (brain and spinal cord) opioid receptors. Consequently, these compounds should also be substantially free of other centrally mediated effects.

In order to determine in vivo opioid receptor antagonism, the mouse writhing analgesis test was used. Test compounds were measured for their ability to block morphine-induced analgesia.

Five CF-1 male mice (Charles River, Portage, Mich.), weighing approximately 20 g after being fasted overnight, were observed simultaneously for the writhing response. The writhing response was defined as a contraction of the abdominal musculature, followed by the extension of the hind limbs, and was induced by the intraperitoneal adminstration of 0.6% acetic acid in a volumne of 1 ml/100 g body weight. The observation period was 10 min. in duration, beginning 5 min. after injection of acetic acid. The percent inhibition of writhing was calculated from the average number of writhes in the control (non-drug) group. Each data point is the mean (±standard error) for five mice. The ED_{50} was defined as the dose of agonist that inhibited mean writhing by 50%. The AD_{50} was defined as the dose of antagonist that reduced the inhibition of writhing produced by a 1.25 mg/kg dose of morphine sulfate to 50%. Each mouse was only used once. All drugs were administered subcutaneously (1 ml/100 g bwt) 20 min. before the injection of acetic acid.

Determinations of peripheral opioid activity were conducted. Mice maintained (6 mice/cage) on 0.01M saccharin water with 1 g/l morphine sulfate for a minimum of 10 days with mice averaging 3.0+ g water/-mouse/day for at least three days are used as subjects. The morphine water was removed 45 min. prior to injection with the proposed opioid antagonist. Initial testing consisted of 5 mice/dose of compound. The antagonist was given by the subcutaneous or oral, route of administration, and the mice were placed in 11–14"×4 7/12 I.D. clear plastic cylinders with white paper towels used for a floor.

The mice were then monitored visually for 30 minutes post-injection for the presence of jumping and of diarrhea. Jumping was scored as positive if at least one jump occurred in 30 min. Diarrhea was scored as positive when feces were moist enough to stain the white paper at the base of the cylinder. After 30 minutes of testing, the mice were placed back in original cages, put back on morphine water, and not tested again for 48 hrs. Lower doses of the antagonist compounds were tested until threshold doses for diarrhea were determined. Diarrhea is a peripherally mediated sign of precipitated opiate abstinence.

The extent of the effect on peripheral activity compared to central activity of the present compounds can be determined by comparing the AD_{50} for the mouse writhing test with the ED_{50} for the mouse diarrhea test. The higher the ratio, the greater the relative antagonism of the peripheral opioid receptors by a particular compound. This ratio for each compound is provided in Table I.

TABLE I

Example No.(1)	AD_{50}(2)	ED_{50}(3)	Ratio(4)
4A	1.08	0.012	9
4B	8.90	0.011	809
5A	1.2	0.06	20
5B	1.6	0.24	7
8A	0.70	0.02	35
8B	0.64	0.012	53
9B	1.50	0.02	75
10	0.54	0.06	9
11	2.4	0.017	141
12	40	0.015	2667
13	>40	0.32	>125
14	>40	0.92	>43
15	>40	0.30	>133
17	>40	0.06	>667
18	>40	0.045	>888
20	32.1	0.004	802
21	>20	0.16	>125
22	>40	0.08	>500
23	>20	0.14	>140
24	>40	0.10	>400
25	11.5	0.29	40
26	7.5	0.03	250
27	15.3	0.30	51
28	>40	0.01	>4000
29	3.9	0.17	23
30	>40	0.017	>2353
31	5.3	0.14	38
32	7.3	0.16	45
33	10.2	0.17	60
34	15.1	0.18	84
35	40	0.06	667
36	3.8	0.32	12
37	3.9	0.09	43
38	>40	0.06	>667
39	11.9	0.66	18
40	4.5	1.30	3.5
41	4.5	0.17	26
42	2.1	0.26	8
43	1.9	0.013	146
44	>40	0.15	>266
45	2.6	0.24	11
46	40	0.07	571
47	40	0.15	267
48	>40	0.10	>400
49	6.08	0.10	61
50	14.3	0.54	26
51	3.8	0.15	25
52	8	0.20	40
53	>40	1.70	>23
54	23	0.02	1150
55	7.5	0.12	63
56	40	0.06	667
57	>40	0.10	>400
59	5.9	0.54	11
60	11.2	0.10	112
61	3.3	0.05	66
62	18.3	0.15	122
63	26	0.29	90
64	>40	0.90	>45
65	2.8	0.92	3
66	14.0	<3.0	<4.7
67	5.5	0.15	36
68	>40	0.23	>174
69	30	1.70	51
71	2.1	0.19	11
73	20	1.73	11
75	5.2	0.073	71

TABLE I-continued

Example No.[1]	AD_{50}[2]	ED_{50}[3]	Ratio[4]
77	>40	1.31	>31
78B	1.6	0.055	29
79	1.7	0.13	13
80	3.9	0.16	24
81	13.2	3.28	4
82	.95	0.055	17
83	0.71	0.04	2
85	9.5	0.05	190
86	>40	0.017	>2353
87	19	0.71	27
88	13.5	0.07	193
89	6.0	>10	<1
90	2.2	0.1	22
91	4.0	0.5	8
92	7.7	.005	1540
93	29.0	.008	3625
94	20	.009	2222
95	2.7	0.19	14
97D*	12.7	0.04	317
97D**	32	0.6	53
97E	8.9***	0.07***	127
98D*	2.9	0.76	4
98D**	15.3	0.06	255
98E	6.2***	0.10***	62

The compounds of the present invention have been found to display excellent activity in an opioid receptor binding assay which measures the affinity of the compounds to to bind to mu receptors. This assay was conducted by the following procedure.

Male Sprague Dawley rats for mu site experiments were sacrificed via decapitation and the brains were removed. The brain tissue, rat whole brain minus cerebellum for mu was homogenized in a Teflon and glass tissue homogenizer. A supernatant I, pellet IV, fraction was frozen in a nitrogen freezer at 1.33 g/ml concentration and stored for not longer than five weeks prior to use. Pellets were rehydrated with physiological buffer prior to use.

For mu sites increasing concentrations of experimental compound, [0.1 to 1000 nanomolar (nM)], Kreb-Hepes buffer pH 7.4, and tritiated naloxone (0.5 nM) (^{3}H ligand) were combined in polystyrene tubes at room temperature. The reaction was initiated by the addition of the resuspended tissue which had been preincubated at 37° C. for 20 minutes. The reaction mixture was incubated in a 37° C. water bath for 20 minutes. The reaction was terminated by rapid filtration, (Brandel Cell Harvestor), through Whatman GF/B glass filters that had been presoaked in Krebs-Hepes buffer pH 7.4. The filters were then washed 2x with 5 ml of ice cold Krebs-Hepes buffer pH 7.4. Washed filters were placed in scintillation vials and 10 ml RedySolv, (Brandel), was added and samples counted in a Searle D-300 beta counter. Means and standard error statistics were calculated for triplicate experimental determinations in certain cases. The incubation time for the reaction mixture was 20 minutes at 37° C.

Ki values were calculated using a minitab statistical program according to the following formula:

$$K_i = \frac{IC_{50}}{1 + \frac{\text{concentration of } ^3H \text{ ligand}}{K_D}}$$

wherein IC_{50} is the concentration at which 50% of the ^{3}H ligand is displaced by the test compounds and K_D is the dissociation constant for the ^{3}H ligand at the receptor site. K_D can be determined as described by Bennett, "Methods in Binding Studies", *Neurotransmitter Receptor Binding*, Yamamura, et al., ed., p. 57-90, Raven Press, N.Y. (1978) incorporated herein by reference.

The results of the evaluation of certain compounds of the present invention in the opioid receptor binding assay are set forth below in Table II. In the Table, column 1 sets forth the Example Number of the compound evaluated, column 2 the Ki value in nanomolar (nM) at the mu receptor and columns 3 and 4 the percent displacement by the test compound at the indicated concentration, i.e., 10 nm or 100 nm.

TABLE II

	[^{3}H] NAL Binding Assay (mu receptor)		
Example	Ki[1]	10 nM[2]	100 nM [2]
4A	1.38	92	98
4B	2.62	83	97
5A	13.80	61	93
5B	1.11	93	99
8A	2.01	88	95
8B	0.27	100	100
9B	0.66	90	93
10	1.17	89	100
11	0.30	81	89
12	1.89	84	94
13	0.43	94	95
14	6.42	87	93
15	1.07	99	100
17	0.43	97	100
18	0.43	97	97
20	0.78	98	100
21	0.45	96	100
22	0.33	100	96
23	1.65	100	96
24	0.45	100	100
25	0.22	100	100
26	1.17	76	91
27	0.91	92	99
28	3.09	86	95
29	2.94	98	100
30	0.42	89	93
31	0.40	100	97
32	0.72	97	100
33	1.19	95	100
34	36.60	78	97
35	0.54	98	100
36	0.47	79	86
37	1.09	93	97
38	0.48	98	99
39	3.75	91	98
40	0.75	95	100
41	0.39	100	100
42	0.57	100	97
43	0.64	98	99
44	0.89	87	94
45	1.28	93	98
46	0.31	99	95
47	2.11	89	95
48	1.82	96	100
49	0.54	98	100
50	1.20	94	100
51	5.43	85	97
52	—	53	92
53	—	2	11
54	2.27	78	98
55	—	83	97
56	0.49	97	98
57	0.50	92	98
59	4.64	88	100
60	1.89	100	100
61	1.91	98	99
62	1.18	89	98
63	2.00	89	100
64	1.23	94	100
65	—	57	95
66	1.96	70	85
67	0.37	79	91
68	1.51	79	86
69	—	57	89
71	0.71	81	94

TABLE II-continued

Example	[3H] NAL Binding Assay (mu receptor) Ki(1)	10 nM(2)	100 nM (2)
73	1.80	84	90
75	1.15	90	99
77	1.35	88	95
78B	—	0	2
79	—	0	15
80	—	0	37
81	—	21	55
82	—	31	73
83	—	52	83
85	—	93	98
86	—	74	91
87	—	94	99
88	—	93	99
89	—	94	99
90	—	93	99
91	—	69	94
92	—	85	97
93	—	81	95
94	—	76	95
95	—	79	94
97D	—	86	99
97E	—	80	90
98D	—	57	92
98E	—	69	87
97D	—	11	70
98D	—	80	96

(1)In nanomoles
(2)% displacement

While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable excipient and at least one compound of the invention. Such compositions contain from about 0.1 percent by weight to about 90.0 percent by weight of a present compound As such, the present invention also provides pharmaceutical formulations comprising a compound of the invention and a pharmaceutically acceptable excipient therefor.

In making the compositions of the present invention, the active ingredient is usually mixed an excipient which can be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it can be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium), and soft and hard gelatin capsules.

Examples of suitable excipients, include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, water, and mineral oil. The formulations can also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention can be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

For oral administration, a compound of this invention is preferably admixed with one or more excipient, and molded into tablets or enclosed in gelatin capsules.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg more usually about 5 to 300 mg of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

In order to more fully illustrate the operation of this invention, the following formulation examples are provided. The samples are illustrative only, and are not intended to limit the scope of the invention. The formulations may employ as active compounds any of the compounds of the present invention. Specific compounds are provided as illustrative with Z, G, X.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Amount Per Capsule	Concentration by Weight (percent)
Z-$NH(CH_2)_2C(O)NH_2$	20 mg	10.0
starch dried	200 mg	43.0
magnesium stearate	10 mg	2.0
	460 mg	100.0

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Capsules each containing 20 mg of medicament are made as follows:

	Amount Per Capsule	Concentration by Weight (percent)
G-$NH(CH_2)_2C(O)NH_2$	20 mg	10.0
starch	89 mg	44.5
microcrystalline cellulose	89 mg	44.5
magnesium stearate	2 mg	1.0
	200 mg	100.0 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve and filled into a hard gelatin capsule.

Formulation 3

Capsules each containing 100 mg of active ingredient are made as follows:

	Amount Per Capsule	Concentration by Weight (percent)
G-$NH(CH_2)_3C(O)NHCH_3$	100 mg	30.0
polyoxyethylene sorbitan monooleate	50 microg	0.02
starch powder	250 mg	69.98
	350.05 mg	100.00

The above ingredients are thoroughly mixed and placed in an empty gelatin capsule.

Formulation 4

Tablets each containing 10 mg of active ingredient are prepared as follows:

	Amount Per Tablet	Concentration by Weight (percent)
X-$OCH_2CH(CH_3)_2$	10 mg	10.0
starch	45 mg	45.0
microcrystalline cellulose	35 mg	35.0
polyvinylpyrrolidone (as 10% solution in water)	4 mg	4.0
sodium carboxymethyl starch	4.5 mg	4.5
magnesium stearate	0.5 mg	0.5
talc	1 mg	1.0
	100 mg	100.0

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granule so produced is dried at 50°–60° C. and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granule which, after mixing, is compressed on a tablet machine to yield a tablet weighing 100 mg.

Formulation 5

A tablet formula may be prepared using the ingredients below:

	Amount Per Capsule	Concentration by Weight (percent)
X-$O(CH_2)_4CH_3$	250 mg	38.0
cellulose microcrystalline	400 mg	60.0
silicon dioxide fumed	10 mg	1.5
stearic acid	5 mg	0.5
	665 mg	100.0

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 6

Suspensions each containing 5 mg of medicament per 5 ml dose are made as follows:

	per 5 ml of suspension
M-$NHCH_2C(O)OH$	5 mg
sodium carboxymethyl cellulose	50 mg
syrup	1.25 ml
benzoic acid solution	0.10 ml
flavor	q.v.
color	q.v.
water	q.s. to 5 ml

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added to the paste with stirring. Sufficient water is then added to produce the required volume.

Formulation 7

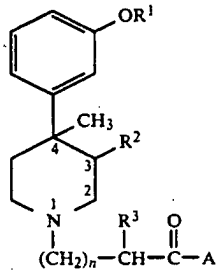
An aerosol solution is prepared containing the following components:

	Concentration by Weight (percent)
U-$NHCH_2C(O)OH$	0.25
ethanol	29.75
Propellant 22 (chlorodifluoromethane)	70.00
	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to −30° C. and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted further with the remaining amount of propellant. The valve units are then fitted to the container.

I claim:

1. A trans-3,4 isomer of a compound of the formula (I)



wherein

R^1 is hydrogen or C_1–C_5 alkyl;

R^2 is hydrogen, C_1–C_5 alkyl or C_2–C_6 alkenyl;

R^3 is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3, alkyl C_5–C_8 cycloalkyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;

A is OR^4 or NR^5R^6;

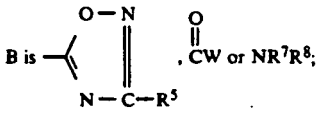
wherein:

R^4 is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;

R^5 is hydrogen or C_1–C_3 alkyl;

R^6 is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, cycloalkyl, phenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, phenyl-substituted C_1–C_3 alkyl, or $(CH_2)_q$—B; or

R^5 and R^6 together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;



, CW or NR^7R^8;

R^7 is hydrogen or C_1–C_3 alkyl;

R^8 is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, cycloalkyl-substituted C_1–C_3 alkyl, cycloalkyl, C_5–C_8 cycloalkenyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, phenyl or phenyl-substituted C_1–C_3 alkyl; or

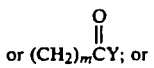
R^7 and R^8 together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;

W is OR^9, $NR^{10}R^{11}$, or OE;

R^9 is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;

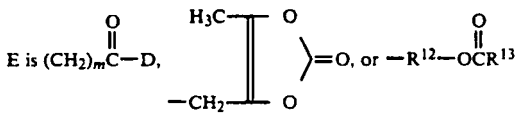
R^{10} is hydrogen or C_1–C_3 alkyl;

R^{11} is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, phenyl-substituted C_1–C_3 alkyl,



or $(CH_2)_mCY$; or

R^{10} and R^{11} together with N form a saturated non aromatic 4- 6-membered heterocyclic ring;



R^{12} is C_1–C_3 alkyl substituted methylene,

R^{13} is C_1–C_{10} alkyl;

D is OR^{14} or $NR^{15}R^{16}$;

wherein:

R^{14} is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, or C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl or phenyl-substituted C_1–C_3 alkyl;

R^{15} is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, phenyl-substituted C_1–C_3 alkyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl or C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl; and

R^{16} is hydrogen or C_1–C_3 alkyl; or

R^{15} and R^{16} together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;

Y is OR^{17} or $NR^{18}R^{19}$;

R^{17} is hydrogen, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, or phenyl-substituted C_1–C_3 alkyl;

R^{18} is hydrogen or C_1–C_3 alkyl; and

R^{19} is hydrogen, C_1–C_{10} alkyl, C_3–C_{10} alkenyl, phenyl, cycloalkyl, C_5–C_8 cycloalkenyl, cycloalkyl-substituted C_1–C_3 alkyl, C_5–C_8 cycloalkenyl-substituted C_1–C_3 alkyl, or phenyl-substituted C_1–C_3 alkyl; or

R^{18} and R^{19} together with N form a saturated non aromatic 4- to 6-membered heterocyclic ring;

n is 0–;

q is 1–4;

m is 1–4;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim **1** wherein R^1 is hydrogen; R^2 is C_1–C_3 alkyl; n = 1 or 2; and R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl.

3. The compound of claim **2** wherein A is OR^4 and R^4 is hydrogen or C_1–C_3 alkyl.

4. The compound of claim **2** wherein A is NR^5R^6 in which R^5 is hydrogen and R^6 is $(CH_2)_q$—B wherein q is 1 to 3 and B is —C(O)W.

5. The compound of claim **4** wherein W is OR^9 and R^9 is hydrogen, C_1–C_5 alkyl, phenyl-substituted C_1–C_2 alkyl, C_5–C_6 cycloalkyl, or C_5–C_6 cycloalkyl-substituted C_1–C_3 alkyl.

6. The compound of claim **4** wherein W is $NR^{10}R^{11}$ in which R^{10} is hydrogen or C_1–C_3 alkyl, and R^{11} is hydrogen, C_1–C_3 alkyl or $(CH_2)_mC(O)Y$.

7. The compound of claim **6** wherein m is 1 to 3 and Y is OR^{17} or $NR^{18}R^{19}$ wherein R^{17}, R^{18} and R^{19} are independently hydrogen or C_1–C_3 alkyl.

8. The compound of claim **4** wherein W is $OCH_2C(O)OD$ in which D is OR^{14} or $NR^{15}R^{16}$ wherein R^{14} is hydrogen or C_1–C_3 alkyl, R^{15} is hydrogen and R^{16} is methyl or benzyl.

9. The compound of claim **4** wherein W is $OR^{12}OC(O)R^{13}$, wherein R^{12} is —$CH(CH_3)$— or —$CH(CH_2CH_3)$— and R^{13} is C_1–C_3 alkyl.

10. The compound of claim **1** wherein the configuration at positions 3 and 4 of the piperidine ring is each R.

11. The compound of claim **1** selected from the group consisting of

$QCH_2CH[CH_2(C_6H_5)]C(O)OH$,

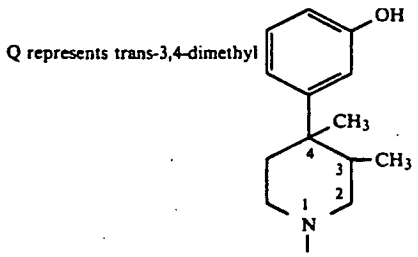
$QCH_2CH_2CH(C_6H_5)C(O)NHCH_2C(O)$-$OCH_2CH_2$, $QCH_2CH_2CH(C_6H_5)C(O)NHCH_2$-$C(O)OH$, Q-$CH_2CH_2CH$-$(C_6H_5)C(O)NHCH_2$-$C(O)NHCH_3$, Q-$CH_2CH_2CH(C_6H_5)C(O)NHCH_2$-$C(O)$-$NHCH_2CH_3$, G-$NH(CH_2)_2C(O)NH_2$, G-$NH(CH_2)_2C(O)NHCH_3$, G-$NHCH_2C(O)NH_2$, G-$NHCH_2C(O)NHCH_3$, G-$NHCH_3C(O)NHCH_2CH_3$, G-$NH(CH_2)_3C(O)OCH_2CH_3$, G-$NH(CH_2)_3C(O)NHCH_3$, G-$NH(CH_2)_2C(O)$-OH, G-$NH(CH_2)_3C(O)OH$,

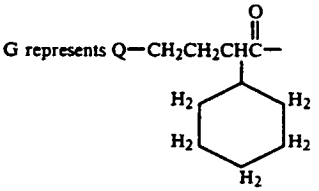
$QCH_2CH[CH_2(C_6H_{11})]C(O)NHCH_2C(O)OH$,

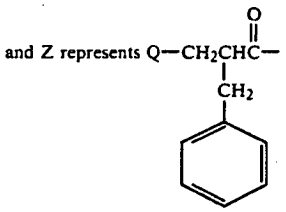
$QCH_2CH[CH_2(C_6H_{11})]C(O)NH(CH_2)_2C(O)OH$,

$QCH_2CH[CH_2(C_6H_{11})]$-$C(O)NH(CH_2)_2C(O)NH_2$,

Z-$NHCH_2C(O)OCH_2CH_3$, Z-$NHCH_2C(O)OH$, Z-$NHCH_2C(O)NH_2$, Z-$NHCH_2C(O)N(CH_3)_2$, Z-$NHCH_2C(O)NHCH(CH_3)_2$, Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, Z-$NH(CH_2)_2C(O)OCH_2(C_6H_5)$, Z-NH-$(CH_2C(O)OH$, Z-$NH(CH_2)_2C(O)NHCH_2CH_3$, Z-$NH(CH_2)_3C(O)NHCH_3$, Z-$NHCH_2C(O)NHCH_2C(O)OH$, Z-$NHCH_2C(O)OCH_2C(O)OCH_3$, Z-$NHCH_2$-$C(O)O(CH_2)_4CH_3$, Z-$NHCH_2C(O)OCH_2$-$C(O)NHCH_3$, Z-$NHCH_2C(O)O$-(4-methoxycyclohexyl), Z-$NHCH_2C(O)OCH_2$-$C(O)NHCH_2(C_6H_5)$, and Z-$NHCH_2C(O)OCH(CH_3)OC(O)CH_3$, wherein:







and pharmaceutically acceptable salts thereof.

12. A compound of claim 11 selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)Z-$NHCH_2C(O)OH$, (—)Z-$NHCH_2C(O)OH$, (3R,4R,R)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,S)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3R,4R)-$ZNHCH_2C(O)NHCH_2(C_6H_5)$ and (3R,4R)-G-$NH(CH_2)_3C(O)OH$, and pharmaceutically acceptable salts thereof.

13. A substantially pure stereoisomer of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical formulation comprising a compound of claim 1 or the salt thereof in combination with a pharmaceutically acceptable excipient.

15. A pharmaceutical formulation comprising a compound of claim 11 or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable excipient.

16. A method for treating irritable bowel syndrome in a patient said method comprising administering to said patient an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

17. A method for binding a peripheral opioid receptor in a patient which comprises administering to said patient an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

18. The method of claim 17 wherein said peripheral effect being treated is constipation, nausea or vomiting.

19. A method for blocking mu receptors in mammals comprising administering to a mammal requiring blocking of a mu receptor a receptor blocking dose of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

20. A method for treating idiopathic constipation in a patient said method comprising administering to said patient an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

21. A method of claim 16 wherein the compound is one wherein R^1 is hydrogen; R^2 is C_1–C_3 alkyl; n=1 or 2; and R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl.

22. A method of claim 21 wherein the compound is one wherein A is NR^5R^6 and R^5 is hydrogen, R^6 is $(CH_2)_q$—B, q is 1 to 3 and B is —C(O)W.

23. A method of claim 22 wherein the compound is one wherein W is OR^9 and R^9 is hydrogen, C_1–C_5 alkyl, phenyl-substituted C_1–C_2 alkyl, C_5–C_6 cycloalkyl, or C_5–C_6 cycloalkyl-substituted C_1–C_3 alkyl.

24. A method for treating irritable bowel syndrome in a patient comprising administering to the patient an effective amount of a compound of claim 11.

25. A method of claim 24 wherein the compound is selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)Z-$NHCH_2C(O)OH$, (—)Z-$NHCH_2C(O)OH$, (3R,4R,R)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,S)-$ZNCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-$ZNHCH_2C(O)OCH_2CH\text{-}(CH_3)_2$, (3R,4R)-$ZNHCH_2C(O)NHCH_2(C_6H_5)$ and (3R,4R)-G-$NH(CH_2)_3C(O)OH$.

26. A method of claim 18 wherein the compound is one wherein R^1 is hydrogen; R^2 is C_1–C_3 alkyl; n=1 or 2; and R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl.

27. A method of claim 26 wherein the compound is one wherein A is NR^5R^6 and R^5 is hydrogen, R^6 is $(C_2)_q$—B, q is 1 to 3 and B is —C(O)W.

28. A method of claim 27 wherein the compound is one wherein W is OR^9 and R^9 is hydrogen, C_1–C_5 alkyl, phenyl-substituted C_1–C_2 alkyl, C_5–C_6 cycloalkyl, or C_5–C_6 cycloalkyl-substituted C_1–C_3 alkyl.

29. A method for binding a peripheral opioid receptor in a patient which comprises administering to said patient an effective amount of a compound of claim 11.

30. A method of claim 29 wherein the compound is one selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)Z-$NHCH_2C(O)OH$, (—)Z-$NHCH_2C(O)OH$, (3R,4R,R)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,S)-$ZNCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-$ZNHCH_2C(O)OCH_2CH\text{-}(CH_3)_2$, (3R,4R)-$ZNHCH_2C(O)NHCH_2(C_6H_5)$ and (3R,4R)-G-$NH(CH_2)_3C(O)OH$.

31. A method of claim 19 wherein the compound is one wherein R^1 is hydrogen; R^2 is C_1–C_3 alkyl; n=1 or 2; and R^3 is benzyl, phenyl, cyclohexyl or cyclohexylmethyl.

32. A method of claim 31 wherein the compound is one wherein A is NR^5R^6 and R^5 is hydrogen, R^6 is $(CH_2)_q$—B, q is 1 to 3 and B is —C(O)W.

33. A method of claim 32 wherein the compound is one wherein W is OR^9 and R^9 is hydrogen, C_1–C_5 alkyl, phenyl-substituted C_1–C_2 alkyl, C_5–C_6 cycloalkyl, or C_5–C_6 cycloalkyl-substituted C_1–C_3 alkyl.

34. A method for blocking a mu receptor in a mammal comprising administering to a mammal requiring blocking of a mu receptor a receptor blocking dose of a compound of claim 11.

35. A method of claim 34 wherein the compound is one selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)Z-$NHCH_2C(O)OH$, (—)Z-$NHCH_2C(O)OH$, (3R,4R,R)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,S)-

$ZNCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-$ZNHCH_2C(O)OCH_2$-$CH(CH_3)_2$, (3R,4R)-$ZNHCH_2C(O)NHCH_2(C_6H_5)$ and (3R,4R)-G-$NH(CH_2)_3C(O)OH$.

36. A method of claim **20** wherein the compound is one wherein R^1 is hydrogen; R^2 is C_1–C_3 alkyl; n=1 or 2; and R^3 is benzyl, phenyl, cyclohexyl, or cyclohexylmethyl.

37. A method of claim **36** wherein the compound is one wherein A is NR^5R^6 and R^5 is hydrogen, R^6 is $(CH_2)_q$—B, q is 1 to 3 and B is —C(O)W.

38. A method of claim **37** wherein the compound is one wherein W is OR^9 and R^9 is hydrogen, C_1–C_5 alkyl, phenyl-substituted C_1–C_2 alkyl, C_5–C_6 cycloalkyl, or C_5–C_6 cycloalkyl-substituted C_1–C_3 alkyl.

39. A method for treating idiopathic constipation in a patient comprising administering to the patient an effective amount of a compound of claim **11**.

40. A method of claim **39** wherein the compound is one selected from the group consisting of (3R,4R,S)-Z-$NHCH_2C(O)OCH_2CH(CH_3)_2$, (+)Z-$NHCH_2C(O)OH$, (—)Z-$NHCH_2C(O)OH$, (3R,4R,R)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,S)-$ZNHCH_2C(O)OCH_2CH(CH_3)_2$, (3S,4S,R)-$ZNHCH_2C(O)OCH_2CH$-$(CH_3)_2$, (3R,4R)-$ZNHCH_2C(O)NHCH_2(C_6H_5)$ and (3R,4R)-G-$NH(CH_2)_3C(O)OH$.

* * * * *

EXHIBIT 4

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,250,542 Page 1 of 10

DATED : October 5, 1993

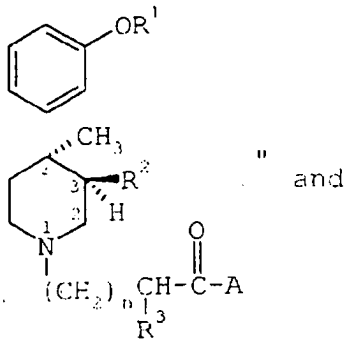
INVENTOR(S) : Buddy E. Cantrell, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2, line 62, delete the term "$\overset{O}{\overset{\|}{C}}Y$" and replace it with --$(CH_2)_n\overset{O}{\overset{\|}{C}}Y$--.

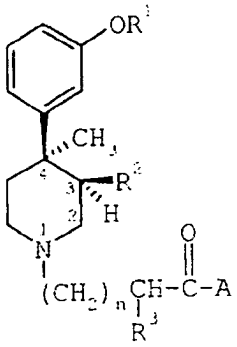
Column 3, line 17, delete the term "C_{10}-C_{16}" and replace it with --(C_1-C_{16})--.

Column 5, lines 1-12, delete the structure "



" and

replace it with --



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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

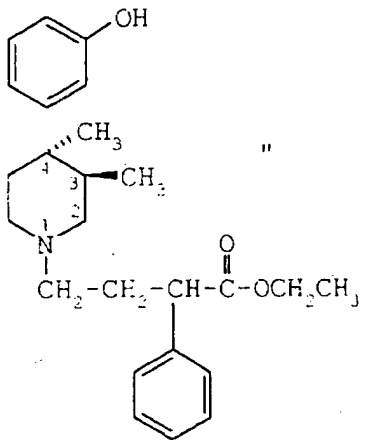
PATENT NO. : 5,250,542

DATED : October 5, 1993

INVENTOR(S) : Buddy E. Cantrell, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 7, lines 12-27, delete the structure

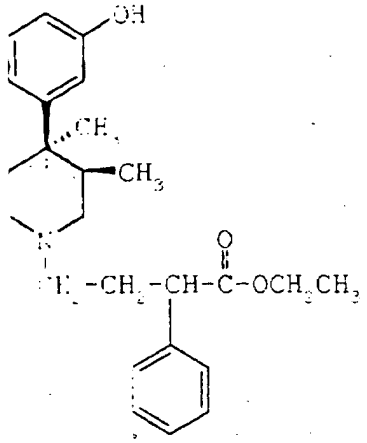


"

"

and replace it with

--



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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,250,542

DATED : October 5, 1993

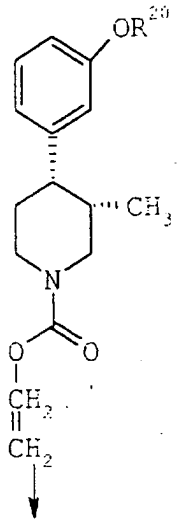
INVENTOR(S) : Buddy E. Cantrell, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8, line 22, delete the term "pheny)" and replace it with --phenyl)--.

Column 13, line 54, delete the term "R^8" and replace it with --R^3--.

Column 13, line 66, delete the term "e-methylene" and replace it with --α-methylene--.

Column 14, lines 1-15, delete the structure "  "

UNITED STATES PATENT AND TRADEMARK OFFICE

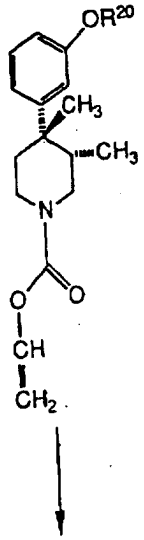
CERTIFICATE OF CORRECTION

PATENT NO. : 5,250,542 Page 4 of 10

DATED : October 5, 1993

INVENTOR(S) : Buddy E. Cantrell, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:



and replace it with -- -- .

Column 17, line 27, delete the term "1,3,8-trimethyl" and replace it with --1,3,4-trimethyl--.

Column 17, line 48, delete the term "$[\alpha]_{589}$" and replace it with --$[\alpha]_{365}$--.

Column 22, line 47, delete the term "$C_{26}H_{35}N_3O \cdot HCl$ and replace it with --$C_{26}H_{35}N_3O_3 \cdot HCl$--.

Column 22, line 63, delete the term "424 $^{+}$+1" and replace it with --424 M^{+}+1--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,250,542

DATED : October 5, 1993

INVENTOR(S) : Buddy E. Cantrell, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 23, line 7, delete the term "U-$NHCH_3C(O)$-$NHCH_2CH_3 \cdot HCl \cdot H_2O$]" and replace it with --[U-$NHCH_2C(O)$-$NHCH_2CH_3 \cdot HCl \cdot H_2O$]--.

Column 23, line 53, delete the term "[G-$NH(CH_3)_2C(O)NH_2 \cdot HCl$]" and replace it with --[G-$NH(CH_2)_2C(O)NH_2 \cdot HCl$].

Column 25, line 21, delete the term "119°-12° C" and replace it with --119°-124°C--.

Column 27, line 9, delete the term "$NHCH_2C(O)OCH_2CH_2 \cdot HCl$]" and replace it with --$NHCH_2C(O)OCH_2CH_3 \cdot HCl$]--.

Column 28, line 67, delete the term "65.0S" and replace it with --65.05--.

Column 29,line 58, delete the term "C, 6%.91" and replace it with --C, 64.91--.

Column 29, line 59, delete the term "C, 6S.04" and replace it with --65.04--.

Column 30, line 17, delete the term " 6S.86" and replace it with --65.86--.

Column 30, line 53, delete the term "444 M+1" and replace it with --444 M^++1--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,250,542

DATED : October 5, 1993

INVENTOR(S) : Buddy E. Cantrell, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 35, line 10, delete the term "[X-O-(CH_6H_{11})·HCl]" and replace it with --"[X-O-(C_6H_{11})·HCl]".

Column 35, line 34, delete the term "3,8-dimethyl" and replace it with --3,4 dimethyl--.

Column 35, line 36, delete the term "[X-OCH_2(CH_6H_{11})·HCl]"and replace it with --[X-OCH_2(C_6H_{11})·HCl]--.

Column 35, line 39, delete the term "(7S0 mg)" and replace it with --(750 mg)--.

Column 36, line 8, delete the term "C_{298}" and replace it with --C_{29}--.

Column 36, line 17 delete the term "[$XOCH_2$(CH_6H_5)·HCl]" and replace it with --[$XOCH_2$(C_6H_5)·HCl]--.

Column 36, line 45, delete the term "[Z-NH(CH_2)$_2$C(O)OCH_2(CH_6H_5)·HCl]" and replace it with --[Z-NH(CH_2)$_2$C(O)OCH_2(C_6H_5)·HCl]--.

Column 37, line 9, delete the term "Hz" and replace it with --H_2--.

Column 38, line 47, delete the term "C_{26}" and replace it with --C_{29}--.

Column 39, line 1, after the term "HCl" add ---·--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,250,542

DATED : October 5, 1993

INVENTOR(S) : Buddy E. Cantrell, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 39, line 9, after the term "monohydrochloride" add --. [Z--.

Column 39, line 21, delete the term "C, [illegible].4" and replace it with --66.44--.

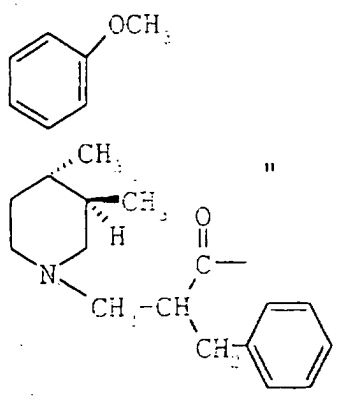
Column 40, line 49, delete the term "C, [illegible]" and replace it with --C, 63.77--.

Column 42, line 28, delete the term "3,4-[illegible]yl-" and replace it with --3,4-dimethyl-1- --.

Column 42, line 60, delete the phrase "$[H_2NCH_2C(O)NHCH_2C(O)NHCH_2C(O)NHCH_2-(C_6H_5]$" and replace it with --$[H_2NCH_2C(O)NHCH_2C(O)NHCH_2-(C_6H_5]$--.

Column 42, line 64, delete the term "t-butoxycarbon-yl" and replace it with --t-butoxycarbonyl--.

Column 45, lines 25-40, delete the structure "



"

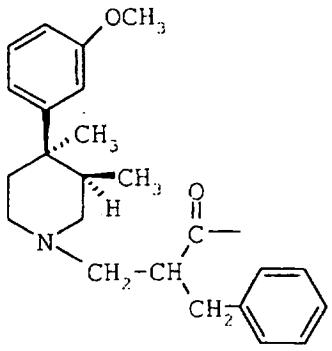
CERTIFICATE OF CORRECTION

PATENT NO. : 5,250,542 Page 8 of 10

DATED : October 5, 1993

INVENTOR(S) : Buddy E. Cantrell, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

and replace it with --  --.

Column 45, line 65, delete the term "(2..72 g) and replace it with --2.72 g)--.

Column 49, line 52, delete the term "218 m9" and replace it with --218 mg--.

Column 49, line 66, delete the term "aceate" and replace it with --acetate--.

Column 51, line 20, delete the term "H, 7.0B;" and replace it with --H, 7.08;--.

Column 51, line 33, delete the term "N_3OH" and replace it with --NaOH--.

Column 53, line 11, delete the term "N_3OH" and replace it with --NaOH--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,250,542

DATED : October 5, 1993

INVENTOR(S) : Buddy E. Cantrell, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 53, line 40, delete the term "57-67" and replace it with --57-65--.

Column 53, line 66, delete the term "ms (fd)'424 M^+," and replace it with --ms (fd) = 424 M^+,--.

Column 55, line 7, delete the term "7.7N 6.32;" and replace it with --7.74 N 6.32;--.

Column 57, line 23, after the [illegible], insert the following

--(1) compound tested corresponding to Example Number
(2) mg/kg in mouse writhing test
(3) mg/kg in mouse diarrhea test
(4) ration of AD_{50} to [illegible]
* Diastereomer A
** Diastereomer B
*** I. V. administration because of lack of sample--.

Column 64, line 1, delete the term "0-;" and replace it with --0-4;--.

Column 64, line 46, delete the term "$NHCH_3C(O)NHCH_2CH_3$," and replace it with -- $NHCH_2C(O)NHCH_2CH_3$

Column 64, line 59, delete the term "$(CH_2C(O)OH$," and replace it with --$(CH_2)_2C(O)OH$,--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,250,542

DATED : October 5, 1993

INVENTOR(S) : Buddy E. Cantrell

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 66, line 22, delete the term "$ZNCH_2C(O)OCH_2CH(CH_3)_2$," and replace it with --$ZNHCH_2C(O)OCH_2CH(CH_3)_2$--.

Column 66, line 32, delete the term "$(C_2)_q$-B," and replace it with --$(CH_2)_q$-B,--.

Column 66, line 45, delete the term "$ZNCH_2C(O)OCH_2CH(CH_3)_2$," and replace it with --$ZNHCH_2C(O)OCH_2CH(CH_3)_2$,--.

Column 67, line 1, delete the term "$ZNCH_2C(O)OCH_2CH(CH_3)_2$," and replace it with --$ZNHCH_2C(O)OCH_2CH(CH_3)_2$,--.

Signed and Sealed this

Twenty-eighth Day of December, 1999

Attest:

Q. TODD DICKINSON

Attesting Officer *Acting Commissioner of Patents and Trademarks*

EXHIBIT 5

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United States Patent and Trademark Office

Patent Bibliographic Data					06/02/2008 11:24 AM
Patent Number:	5250542		**Application Number:**	07916783	
Issue Date:	10/05/1993		**Filing Date:**	07/17/1992	
Title:	PERIPHERALLY SELECTIVE PIPERIDINE CARBOXYLATE OPIOID ANTAGONISTS				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	04/04/2005 03/29/2001 03/03/1997	Payment of Maintenance Fee, 12th Year, Large Entity. Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
Address for fee purposes:	ATTENTION: PATENT DIVISION ELI LILLY AND COMPANY LILLY CORPORATE CENTER INDIANAPOLIS, IN 46285				

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United States Patent and Trademark Office

Patent Maintenance Fees			06/02/2008 11:25 AM EDT
Patent Number:	5250542	Application Number:	07916783
Issue Date:	10/05/1993	Filing Date:	07/17/1992
Window Opens:		Surcharge Date:	
Window Closes:		Payment Year:	
Entity Status:	LARGE		
Customer Number:	000000		
Street Address:	ATTENTION: PATENT DIVISION ELI LILLY AND COMPANY		
City:	INDIANAPOLIS		
State:	IN		
Zip Code:	46285		
Phone Number:	(000) 000-0000		
Currently there are no fees due.			

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EXHIBIT 6

MWT OCT 21 '93

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 43,693

OCT 18 1993

Eli Lilly and Company
Attention: M.W. Talbott, PhD
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Talbott:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 43,693

Sponsor: Eli Lilly and Company

Name of Drug: LY246736 Dihydrate Capsules

Date of Submission: October 11, 1993

Date of Receipt: October 12, 1993

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon

as possible and in no event later than 10 working days after initial receipt of information; reporting any unexpected fatal or life-threatening experience to FDA by telephone no later than three working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Attention: Document Control Room 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this submission, please call me at (301) 443-0487.

Sincerely yours,

Kati Johnson

Kati Johnson
Consumer Safety Officer
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center of Drug Evaluation and Research

EXHIBIT 7

Lilly

3613.3

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

COPY

February 3, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Attn.: Document Control Room 6B-24
5600 Fishers Lane
Rockville, Maryland 20857-1706

IND 43,693 - Compound LY246736 Dihydrate Capsules
Serial No.: 013

This correspondence is to notify you that on November 5, 1996, Eli Lilly and Company entered into an agreement with Roberts Laboratories Inc., a wholly owned subsidiary of Roberts Pharmaceutical Corporation, granting them the right to development of the aforementioned compound. Consequently, Eli Lilly and Company is transferring sole sponsorship of IND 43,693 to Roberts effective February 1, 1997. Roberts will assume all responsibilities of maintaining the IND and will be the official correspondent for any future communications with the FDA. All records have been transferred from Lilly to Roberts. There are no ongoing clinical trials at this time.

Please address any questions you may have for Lilly to Dr. Kelly Freeman at (317) 276-1337. Questions for Roberts should be addressed to Mr. Drew Karlan at (908) 389-1182. Thank you for your continued assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Enclosures

GTB:dmm

EXHIBIT 8

ROBERTS PHARMACEUTICAL CORPORATION

June 24, 1998

Lilia Talarico, M.D.
FOOD AND DRUG ADMINISTRATION
CDER, DGICDP (HFD-180)
Attn: Document Control Rm. 6B-24
5600 Fishers Lane
Rockville, MD 20857

IND 43,693: LY246736 Dihydrate Capsules
Serial No. 017: Letter of Authorization to IND

Dear Dr. Talarico:

This letter authorizes the Food and Drug Administration to refer to IND 43,693, for LY246736 Dihydrate Capsules, on behalf of ADOLOR Corporation, 371 Phoenixville Pike, Malvern, PA 19355.

ADOLOR Corporation intends to submit their own IND for the purpose of conducting Phase I clinical studies under a licensing agreement with Roberts Laboratories Inc.

This authorization will remain in effect for a period of one calendar year from the date of this letter.

If you have any questions regarding this letter, please do not hesitate to communicate with me.

Sincerely,

Drew Karlan

Drew Karlan, V.P.
Worldwide Regulatory Affairs

DR/lb

Enclosure: FORM FDA 1571
c: Mr. Richard Olson (ADOLOR Corporation)

LY736LOA.FDA

EXHIBIT 9

ROBERTS PHARMACEUTICAL CORPORATION

June 17, 1999

COPY

Lilia Talarico, M.D.
FOOD AND DRUG ADMINISTRATION
CDER, DGICDP (HFD-180)
Attn: Document Control Rm. 6B-24
5600 Fishers Lane
Rockville, MD 20857

IND 43,693: LY246736 Dihydrate Capsules
Serial No. 019: Letter of Authorization to IND

Dear Dr. Talarico:

This letter authorizes the Food and Drug Administration to refer to IND 43,693, for LY246736 Dihydrate Capsules, on behalf of ADOLOR Corporation, 371 Phoenixville Pike, Malvern, PA 19355.

This authorization will remain in effect for a period of one calendar year from the date of this letter.

If you have any questions regarding this letter, please do not hesitate to communicate with me.

Sincerely,

Alvin Howard, Vice President
Worldwide Regulatory Affairs

AH/lep

Enclosure: FORM FDA 1571
c: Mr. Richard Olson (ADOLOR Corporation)

EXHIBIT 10

ROBERTS
RMACEUTICAL
CORPORATION

COPY

March 22, 2000

Lilia Talarico, M.D.
FOOD AND DRUG ADMINISTRATION
CDER, DGICDP (HFD-180)
Attention: Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

IND 43,693: LY246736 Dihydrate Capsules
Serial No. 021: Transfer of IND Ownership to ADOLOR Corporation

Dear Dr. Talarico:

This letter authorizes the Food and Drug Administration to transfer all rights to IND 43,693 (LY246736 Dihydrate Capsules) from the existing holder of the IND, Roberts Laboratories Inc. to ADOLOR Corporation, 371 Phoenixville Pike, Malvern, PA 19355.

There has been no activity regarding IND 43,693 since Roberts acquired the rights to this product from Eli Lilly & Co. on February 1, 1997. There are no ongoing clinical trials and no patients are on therapy with LY246736 Dihydrate Capsules under this IND. The last Annual Report was submitted to the IND on March 3, 1999 (Serial No. 018).

If you have any questions regarding this letter, please do not hesitate to communicate with me at (732) 676-1200, ext. 2074.

Sincerely,

Alvin Howard, Vice President
Regulatory Affairs

RR\lep
Enc.: FORM FDA 1571
c: Mr. Richard Olson (ADOLOR Corporation)

LY736transfer

EXHIBIT 11

adolor CORPORATION

343 Phoenixville Pike, Malvern, PA 19355 TEL (610) 889-3470 FAX (610) 889-5760

September 21, 2000

Lilia Talarico, M.D., Director
Division of Gastrointestinal and
Coagulation Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-180
5600 Fishers Lane
Rockville, MD 20857

RE: IND #43,693
Serial No. 023 - **Response to FDA Request for Information**

Dear Dr. Talarico:

Sponsorship of the referenced IND was transferred from Roberts Laboratories, Inc. to Adolor Corporation on March 22, 2000, in Serial No. 021. On March 29, 2000, in Serial No. 022, Adolor accepted all agreements, promises and conditions made by Roberts that were still in effect at the time of the transfer. Pursuant to that transfer and acceptance, Mr. Paul Levine requested on September 12, 2000, the following information to complete the change of sponsorship procedure. His request is highlighted below with our response.

1. **"A commitment to inform all active investigators of the change in sponsorship and to obtain from them updated forms FDA 1572 and commitments to you as the new sponsor."**

Adolor does commit to inform all active investigators of the change in sponsorship and to obtain from them updated forms FDA 1572 and commitments to us as the new sponsor. However, Roberts withdrew this IND in Serial No. 20 on December 3, 1999, and there were no active investigators or study subjects taking the investigational drug at the time of the transfer for Adolor to notify. The IND has not been reactivated nor amended to provide for clinical trials and active investigations.

2. **"A list of all active investigators or a statement that they are the same as currently listed in the IND, if that is the case."**

As noted above, there are no active investigators in the withdrawn IND. Adolor has not amended the IND other than to accept the transfer. There have been no additions or deletions of the investigators, as no studies are being conducted under this IND. The last annual report prior to Robert's withdrawal of the IND stated that there had been no activity conducted under the IND during the report period of April 8, 1998 through September 30, 1998 (please refer to Serial No. 018: Annual Report). This IND has been used by Adolor as reference only.

3. "Submission of any change in protocol or other study parameters."

When the investigational compound, LY246736 Dihydrate capsules, was licensed to Adolor for development, Adolor filed its own IND, No. 56,533, which is currently active and refers to the investigational drug as ADL 8-2698. The Roberts IND No. 43,693 (formerly sponsored by Eli Lilly & Co.) was referenced in Adolor's IND filing. Thus, Adolor made no change to protocols originally filed to the Roberts IND. If Adolor's clinical studies under its IND progress to an NDA, any relevant sections and reports from IND 43,693 will be filed in the NDA.

If you have any questions or need additional information, please contact me at 610-889-3472 by phone or 610-889-5760 by facsimile.

We understand that this IND and all information contained therein, unless otherwise made public by Adolor Corporation, is CONFIDENTIAL.

Sincerely,

ADOLOR CORPORATION

Linda Y. Harver

Linda Y. Harver, R.Ph., J.D.
Vice President, Regulatory Affairs

EXHIBIT 12

CONFIDENTIAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 7, 2004

To: Linda Harver, R.Ph., J.D.	**From:** Melissa Hancock Furness Regulatory Health Project Manager
Company: Adolor Corporation	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 484-595-1528	**Fax number:** 301-443-9285
Phone number: 484-595-1011	**Phone number:** 301-827-~~4005~~ 7450
Subject: Filing Letter, NDA 21-775	
Total no. of pages including cover:	

Comments: Please find attached a copy of your Filing Letter for Entereg (Alvimopan) Capsules. In addition, please note that your Application has been classified as a Standard review, therefore, your PDUFA goal date will be April 25, 2004.

Should you have questions, please contact me at 301-827-7450.

Best regards.

Document to be mailed: √ YES NO

CONFIDENTIAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-775

Adolor Corporation
Attention: Linda Y. Harver, R.Ph., J.D.
700 Pennsylvania Drive
Exton, PA 19341

Dear Ms. Harver:

Please refer to your June 25, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entereg (Alvimopan) Capsules.

We also refer to your submissions dated May 4, 2004 and May 27, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 24, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues from an overview of the submission:

1) It appears that 12 mg of Entereg demonstrated statistical significance over placebo in the primary efficacy endpoint [the time to tolerate the first solid meal and (the time to the first bowel movement or first flatus)] in only one (313) of the four Phase III efficacy trials (302, 308, 313, and 306).

2) It appears that 12 mg of Entereg demonstrated statistical significance over placebo in a secondary endpoint (time to discharge written) in only two (313 and 308) of the four Phase III efficacy trials.

3) In Trial 313, the demonstration of a positive primary efficacy endpoint may have been due to the poor placebo response.

Therefore, we are concerned that the efficacy results for 12 mg of Entereg may not be adequate for the proposed indication.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions, call Tanya Clayton, B.S., Regulatory Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Director
Division of Gastrointestinal & Coagulation
Drug Products, HFD 180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joyce Korvick
9/7/04 03:20:40 PM

EXHIBIT 13

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-775

NDA APPROVAL

Adolor Corporation
Attention: Linda G. Young, R.Ph., J.D.
Vice President, Regulatory Affairs
700 Pennsylvania Drive
Exton, PA 19341-1127

Dear Ms. Young:

Please refer to your new drug application (NDA) dated August 9, 2007, received August 10, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Entereg (alvimopan) Capsules, 12 mg.

We acknowledge receipt of your submissions dated January 18, October 18, December 18 and 28, 2007, January 10, 17, 25, February 7, March 5 and 6, April 15, 17, 22, 29, and May 1, 2, 14, and 20, 2008.

The August 9, 2007 submission constituted a complete response to our November 3, 2006 action letter.

A meeting of FDA's Gastrointestinal Drugs Advisory Committee was held on January 23, 2008 to discuss the safety and effectiveness of Entereg.

This new drug application provides for the use of Entereg (alvimopan) Capsules, 12 mg, for the acceleration of time to gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred or inapplicable.

We are deferring submission of your pediatric studies for ages 0 months to 16 years until after the completion of your postmarketing required study, which is scheduled for completion

December 31, 2012, because this product is ready for approval in adults and additional safety data in adults are needed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these required postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1. Conduct a study of Entereg for the acceleration of gastrointestinal recovery in pediatric patients age greater than 1 month up to 16 years undergoing bowel resection surgery. The study will measure the time to first tolerated feed, population pharmacokinetic parameters, the proportion of postoperative days with stool passed while in hospital, length of hospital stay, the need for postoperative nasogastric tube insertion for symptoms of postoperative ileus, and safety.

Protocol Submission:	December 2012
Study Start:	June 2013
Final Report Submission:	June 2016

2. Conduct a study of Entereg for the acceleration of gastrointestinal recovery in pediatric patients age 0 to 1 month undergoing bowel resection surgery. The study will measure population pharmacokinetic parameters, safety, and time to first tolerated feed while in the hospital.

Protocol Submission:	December 2016
Study Start:	June 2017
Final Report Submission:	June 2019

Submit all final study reports to your NDA. Use the following designator to prominently label all submissions:

Required Pediatric Assessment

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk, that is, an imbalance in the number of myocardial infarctions in Entereg-treated patients receiving long-term treatment for opioid-induced bowel dysfunction.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is therefore not sufficient to assess a serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this signal of a serious risk of, and to monitor the incidence of, myocardial infarctions in Entereg-treated patients undergoing surgery compared to patients receiving a placebo.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct a clinical trial.

You are required to conduct the following clinical trial:

1. A multi-center, double-blind, placebo-controlled, parallel group clinical trial of Entereg for the management or postoperative ileus in patients undergoing radical cystectomy.

The timetable you submitted on April 22, 2008 states you will conduct this trial according to the following timetable:

Protocol Submission:	June 2008
Trial Start:	March 2009
Final Report Submission:	June 2012

Submit the protocol to your IND 56,553 with a cross-reference letter to this NDA 21-775. Submit all final report(s) to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

Required Postmarketing Protocol under 505(o)
Required Postmarketing Final Report under 505(o)
Required Postmarketing Correspondence under 505(o)

You are required to report periodically to FDA on the status of this postmarketing study pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 314.81. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with Entereg.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amended the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

In accordance with 505-1 of the FDCA, we have determined that a REMS is necessary for Entereg (alvimopan) Capsules, 12 mg, to ensure that the benefits of the drug outweigh the risks of myocardial infarction. Pursuant to section 505-1(f)(1), we have also determined that Entereg can be approved only if the elements necessary to assure safe use are required as part of a REMS to mitigate a specific serious risk, myocardial infarction, listed in the labeling of the drug.

Your proposed REMS, submitted on May 14, 2008 and resubmitted May 20, 2008, and appended to this letter, is approved. The REMS consists of a communication plan, elements to assure safe use, an implementation system, a timetable for assessments, and assessments of the REMS.

Use the following designator to prominently label all submissions, including supplements, relating to this REMS:

Risk Evaluation and Mitigation Strategy (REMS) Submission

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-775."

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your May 1, 2008 submission containing final printed carton and container labels.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We acknowledge your May 2, 2008 commitment to expedited reporting of ischemic cardiovascular events, defined as: acute myocardial infarction, new onset or unstable angina, congestive heart failure, congestive cardiac failure, cerebrovascular accident (CVA), transient ischemic attach (TIA), cardiac arrest, and sudden death.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Beitz
5/20/2008 02:44:17 PM

EXHIBIT 14

Supplement to Response (11): Chronological Listing of Significant Activities Undertaken by the Marketing Applicant During the Applicable Regulatory Review Period With Respect to the Approved Product

Date	IND/NDA	Serial or Amendment #	Activity
10/11/1993	IND 43,693		Lilly submission of IND for LY246736 Dihydrate.
10/12/1993	IND 43,693		FDA letter of October 18, 1993 acknowledging receipt of IND 43,693 on October 12, 1993.
11/11/1993	IND 43,693		Effective date of IND 43,693 under § 505(i)
01/25/1994	IND 43,693		FDA letter to Lilly suggesting amendment to clinical protocol.
02/09/1994	IND 43,693	#001	Pg. 2163 – Amendments a & b to the Dose-Escalation Safety Trial.
02/09/1994	IND 43,693	#002	Lilly letter responding to FDA January 25, 1994 letter requesting modification of Phase I dose-escalation study to allow for 48 hours between single escalating doses, further stating that the clinical study had already been partially completed without incident.
05/16/1994	IND 43,693		Protocol amendment and notice of new investigator, including highlights of results of prior protocol.
05/16/1994	IND 43,693	#003	Pg. 2185 – New Protocol No. H3G-LC-BGGB: "Dose-Escalation Trial in Patients with Irritable Bowel Syndrome."
05/19/1994	IND 43,693	#004	Pg. 2219-ADME Report No. 7: "Plasma Concentrations of LY246736 Following the Oral Administration of LY246736 Dihydrate to Fischer 344 Rats".
08/12/1994	IND 43,693	#005	Pg. 2229 – New Protocol No. H3G-LC-BGGC: "LY246736 – Multiple-Dose Trial in Subjects with Loperamide-Induced Constipation".
12/08/1994	IND 43,693	#006	Pg. 2264 – "Information Amendment: Pharmacology/Toxicity" - Toxicology Report No. 14: "A combined Segment I and Segment II Study of LY246736 Dihydrate Administered Orally to CD Rats". (Study No. R12693 and R12793)
01/06/1995	IND 43,693	#007	Annual report for the period ending November 10, 1994, noting that 3 protocols had been submitted, 2 trials completed and 2 clinical pharmacology trials were started and completed by November 10, 1994.
01/12/1995	IND 43,693		Notice from FDA of late annual report by Lilly.

Date	IND/NDA	Serial or Amendment #	Activity
01/27/1995	IND 43,693	#008	Response by Lilly noting that postal delays caused late receipt of annual report.
05/01/1995	IND 43,693		FDA letter to Lilly recommending that histological and reproductive toxicity studies be conducted.
06/05/1995	IND 43,693	#009	ADME Report No. 10 "A Plasma Concentration of LY246736 Dihydrate to DC-Mice" (Study No. M08894).
01/08/1996	IND 43,693	#010	Annual report for the period ending 11/10/95 period, noting that reproductive toxicity studies and other non-clinical studies had been conducted during the year. The report notes that "No clinical work on LY246736 has been conducted in the last year, and no further work is planned at this time. The decision to suspend further development was based on a reassessment of overall sponsor research goals. Barring transfer of the IND to another sponsor, Lilly will be considering withdrawal of the IND in the next year."
11/05/1996	IND 43,693		Date of Agreement between Lilly and Roberts, granting Roberts the right to develop LY246736 Dihydrate Capsules, as noted in Lilly letter of February 3, 1997.
11/20/1996	IND 43,693		Information Amendment: Pharmacology/Toxicology. [Submission of Tox Report No. 14]
01/08/1997	IND 43,693		Annual Report for 11/10/95 – 11/9/96 period stating, "No preclinical or clinical studies have been conducted during the past year and none are anticipated at this time."
01/21/1997			Receipt of Lilly Documentation by Roberts
02/01/1997	IND 43,693		Lilly transfers sole sponsorship of IND 43,693 to Roberts.
02/03/1997	IND 43,693		Notification to FDA of Lilly transfer of sole sponsorship of IND 43,693 to Roberts on November 5, 1996; that all records had been transferred to Roberts; and that there are no ongoing clinical trials at this time.
02/03/1997			Lilly's notice to FDA transferring IND to Roberts as of 2/1/97
02/12/1997	IND 43,696		Robert's notice to FDA accepting transfer of Lilly IND
02/12/1997	IND 43,696		Lilly letter to FDA providing information regarding February 3, 1997 transfer of all rights and obligations to IND 43,693 to the new sponsor, Roberts.

Date	IND/NDA	Serial or Amendment #	Activity
03/03/1997	IND 43,693		Lilly notification to FDA of transfer of sponsorship of IND 43,693 to Roberts Laboratories, a wholly owned subsidiary of Roberts Pharmaceutical Corporation, now Shire Pharmaceutical Group.
03/06/1997	IND 43,693		FDA response to letter of notification of 2/12/97 of transfer to Roberts.
03/12/1997	IND 43,693		Lilly letter to FDA committing to amend IND to cover any changes resulting from new ownership.
04/21/1997			Lilly ships 41 boxes of written materials to Roberts
04/25/1997			List of materials received by Roberts from Lilly on 04/24/97
08/18/1997			Lilly IND application archived at Roberts (6 volumes)
09/03/1997			Adolor Corp. Chemical Data Sheet: Adolor No. ADL-01-0261-6 (LY246736 (mu antagonist)
01/23/1998			Lilly ships 36 gm samples to Roberts
02/23/1998			Adolor identified LY246736 / Roberts in-licensing opportunity
03/12/1998			Adolor memo on LY246736 synthesis, formulation, clinical trials and safety issues.
03/12/1998			Adolor meeting at Roberts, discussing license to LY246736
03/31/1998	43,693		FDA request for annual report.
04/07/1998	43,693		Annual Report covering 2/1/98 – 4/7/98; Roberts states that the "last annual report that was prepared by Eli Lilly & Co. was submitted to the agency on January 6, 1995 for the review period ending November 10, 1994 (Serial No. 007)," and that "there has been no activity regarding this IND since Roberts acquired the rights to this product on February 1, 1997," and further stating that "there are no ongoing clinical trials and no patients are on therapy with LY246736 Dihydrate Capsules." Roberts states, however, that "we wish to keep this IND in an active status in the event that Roberts initiates clinical trials with the drug."
05/20/1998			Adolor review of Phase 1 of IND application complete
05/21/1998			Lilly reevaluation of expired lots of LY246736 (5/11/98); letter to Roberts
05/26/1998			Continuing Adolor review of Lilly LY246736 dihydrate IND documents (at Adolor).

Date	IND/NDA	Serial or Amendment #	Activity
05/26/1998			Adolor discussion with Roberts about bulk drug manufacturing
05/28/1998			Lilly fax with results of re-analysis of LY246736 by Lilly
05/28/1998			Adolor internal discussions including clinical study design issues, doses, capsules
06/01/1998			Adolor discussions and transmittal of confidential disclosure to prospective manufacturer of capsules, requesting proposal for manufacture of 0.125, 1.0, 6.0 mg and placebo strengths.
06/01/1998			Contacted UPM again about the new Adolor project and their interest in manufacturing clinical supplies. (Also separately contacted PMRS.)
06/01/1998			Discussions & prep for due diligence visit
06/03/1998			Adolor visit to Roberts for review of documentation & samples
06/10/1998	IND 43,693		Adolor entered into an Option and License Agreement with Roberts for a sublicense of all rights for the development and commercialization of LY246736 (subject of IND 43,693)
06/24/1998	IND 43,693		Roberts letter to FDA authorizing FDA to refer to IND 43,693 on behalf of Adolor.
06/29/1998			Adolor telephone discussions with Lilly; confirmed Lilly did file Annual Report January 8, 1997 and requested two boxes of information from corporate storage; requested Lilly tox and drug metabolism information on urgent basis.
06/30/1998			Adolor telephone discussion with Roberts; Roberts will give letter of authorization to their IND for one year; Roberts requested that Adolor open own IND with own protocol, and refer to Roberts IND for preclinical/safety etc.; sponsorship cannot be transferred now, not until option period goes to full license.
07/01/1998			Schmidt telephone discussions including Roberts to fax authorization to Lilly to release data to ADL per license agreement.

Date	IND/NDA	Serial or Amendment #	Activity
07/07/1998			Arrangements finalized between Adolor and UPM to have UPM prepare GMP clinical supplies of ADL 8-2698; facsimile requesting Roberts to ship all materials listed in Roberts "Chemical Inventory for LY246736-Dihydrate Project" to UPM.
07/09/1998			Roberts ships 50+ samples of LY246736 & related materials to UPM on behalf of Adolor
08/03/1998	IND 56,553	#000	Adolor filed IND application for investigational drug ADL 8-2698 (Adolor's name for LY246736).
08/07/1998	IND 56,553		Letter from FDA confirming receipt of IND August 5, 1998.
09/01/1998	IND 56,553		FDA telephone contact regarding need for CMC information, which is not available, and discussion of options regarding IND submission options, withdraw, inactivate or clinical hold.
09/02/1998	IND 56,553	#001	Phone Call to request review date if IND was withdrawn or inactivated so CMC info could be sent; Adolor agrees to inactivate and resubmit with CMC data; follow letter to FDA.
09/02/1998	IND 56,553	#002	Adolor request for inactive status for IND 56,553
09/22/1998	IND 56,553		FDA letter placing Adolor IND 56,553 on inactive status.
10/06/1998	IND 56,553	#003	Adolor letter: Request reactivate and list of modifications to IND
10/23/1998	IND 56,553		FDA letter referring to letters of 09/22/98 and 10/6/98, accepting IND with statement that clinical trials can begin 30 days from receipt (October 7, 1998) of request to reactivate
12/17/1998	IND 56,553	#004	Protocol Amendment: Change in Protocol regarding 98-CP001 "An Ascending Dose Safety Study of ADL 8-2698 (LY246736) in Humans."
03/03/1999	IND 43,693		Roberts annual report noting no activity conducted under IND 43,693 during the report period of April 8, 1998 through September 30, 1998
04/06/1999	IND 56,553	#005	Protocol Amendment: New Protocol regarding 99-CP006 "A Phase I Study Assessing Use of a Peripherally Selective μ Opioid Antagonist . . ."
05/24/1999	IND 56,553	#006	Protocol Amendment: New Protocol/New Investigator regarding 99-CP007 "A Phase I, Double-Blind, Placebo-Controlled, Dose Ranging Study . . ."

Date	IND/NDA	Serial or Amendment #	Activity
06/14/1999	IND 56,553	#007	Protocol Amendment: New Protocol/New Investigator regarding 13C109 "A Double-Blind, Randomized Placebo-Controlled Study of the effect of ADL 8-2698 on Opioid . . ."
06/17/1999	IND 43,693		Roberts letter to FDA authorizing FDA to refer to IND 43,693 on behalf of Adolor.
07/12/1999	IND 56,553	#008	Protocol Amendment: New Protocol/New Investigator regarding 99-CT002 "A Phase II Study Assessing Use of a Peripherally Selective μ Opioid Antagonist . . ."
08/17/1999	IND 56,553	#009	Protocol Amendment: Change in Protocols regarding RC-99-CT001 "A Phase I Study Assessing Use of a Peripherally Selective μ Opioid . . ."
08/24/1999			Transfer of all LY246736 documents to Adolor
10/11/1999	IND 56,553	#010	Annual Report covering the period of October 7, 1998 to September 1, 1999, including updates on Phase 1 and 2 studies conducted during the year.
10/15/1999	IND 56,553	#011	Protocol Amendment: Change in Protocols regarding RC-99-CT002 "A Phase II Study Assessing Use of a Peripherally Selective μ Opioid Antagonist . . ."
11/23/1999	IND 56,553	#015	IND Safety Report.
12/01/1999	IND 56,553	#012	New Protocol/New Investigator regarding 13C206 "A Phase II Double-Blind, Placebo-Controlled, Parallel Study of Efficacy . . ."
12/03/1999	IND 43,693	#020	Roberts letter to FDA withdrawing IND 43,693, noting that "the investigational drug has been licensed to ADOLOR Corporation . . . and will be researched under the ADOLOR Corporation's IND application;" and confirming that "there has been no activity regarding IND 43,693 since Roberts acquired the rights to this product from Lilly on February 1, 1997, and that there are no ongoing clinical trials and no patients are on therapy.
01/13/2000	IND 56,553	#013	Protocol Amendment: New Protocol/New Investigator regarding Protocol 13C208 regarding "A Phase II, Multicenter, Double-Blind, Randomized, Placebo-Controlled . . ."
01/19/2000	IND 56,553	#040	Request for End of Phase II Meeting – CMC.
02/01/2000	IND 56,553	#014	Protocol Amendment: New Protocol/New Investigator regarding Protocol 13C111 "Phase I Randomized, Double-Blind, Placebo-Controlled, Crossover . . ."

Date	IND/NDA	Serial or Amendment #	Activity
02/28/2000			Transfer of LY246736 documents from Roberts to Adolor
03/08/2000	IND 43,693		Telephone contact from FDA regarding "Withdrawal of Original Lilly IND (43,693) by Roberts Serial Number of SAE"
03/13/2000	IND 56,553	#016	Protocol Amendment: Change in Protocols regarding 13C206 Amend. 2: "A Phase II, Double Blind, Placebo-Controlled, Parallel Study of Efficacy . . ."
03/16/2000	IND 43,693		Telephone contact from Maryann Cherubini (MC), Clinical Program Director, to Alice Kacuba (AK), CSO-FDA, regarding "Transfer of Original Lilly IND (43,693) to Adolor."
03/22/2000	IND 43,693	#021	Roberts letter to FDA transferring all rights to IND 43,793 to Adolor, noting that there has been no activity regarding IND 43, 693 since Roberts acquired the rights to this product from Eli Lilly & Company on February 1, 1997; that there are no ongoing clinical trials and no patients are on therapy with LY246736 Dihydrate Capsules under this IND; and that the last Annual Report was submitted to the IND on March 3, 1999.
03/29/2000	IND 43,693	#022	Adolor Letter accepting all agreements, promises and conditions made by Roberts that were still in effect at the time of the transfer.
04/13/2000	IND 56,553	#017	Protocol Amend: New Protocols etc., regarding 13C212 "Force Titration – Chronic Methadone Therapy for Opioid Addiction . . ."
06/09/2000	IND 56,553	#018	Protocol Amendment: Change in Protocol regarding 13C208, "Single Dose, Chronic Opioid Therapy for Pain or Opioid Addiction . . ."
07/13/2000	IND 56,553	#019	Request for Type B Meeting
07/13/2000	IND 56,553	#020	Information Amendment regarding "A Chronic Tox Study in Fischer 344 Rats Given LY246736 Dihydrate . . ."
08/07/2000	IND 56,553	#021	Protocol Amendment: New Protocol etc. regarding 13C214 "Postoperative Opioid-Induced Bowel Dysfunction . . ."
09/06/2000	IND 56,553	#022	Information Amendment regarding Protocol 13C109.
09/12/2000	IND 43,693	#023	FDA letter to Adolor requesting further information to complete change in sponsorship of IND 43,693.

Date	IND/NDA	Serial or Amendment #	Activity
09/13/2000	IND 56,553	#023	Pre-Meeting Package (Briefing Document).
09/21/2000	IND 43,693		Adolor letter to FDA providing requested information regarding transfer of sponsorship of IND 43,693 from Roberts to Adolor on March 22, 2000, noting, *inter alia*, that investigational compound LY246736 Dihydrate Capsules was licensed to Adolor for development; that Adolor filed its own IND 56,533, which is currently active and refers to the investigational drug as ADL 8-2698; that Roberts' (formerly Lilly's) IND 43,693 was referenced in Adolor's IND filing; and that any relevant sections and reports from IND 43,693 will be filed in the NDA.
10/03/2000	IND 56,553	#024	Information Amendment: Final Clinical Study Report.
10/03/2000	IND 56,553	#025	Protocol Amendment: New Protocol etc. regarding 13C213 "A multicenter Phase II/III, Double-Blind, Dose Ranging, Placebo-Controlled . . ."
10/03/2000	IND 56,553	#026	Information Amendment; CMC, regarding CMC Request for Comments.
10/16/2000	IND 56,553	#030	Adolor and FDA face to face meeting to discuss clinical development plan and proposed endpoints of study; facsimile including slides from meeting, slides assigned serial #030
10/26/2000	IND 56,553	#027	Information Amendment: Clinical Protocol Amendment, to provide for a revised clinical investigator's brochure etc.
11/15/2000	IND 56,553	#028	Protocol Amendment; "New Investigator information for protocol 12C213. . ."
11/15/2000	IND 56,553	#029	General Correspondence; New Corporate Address for Adolor
12/14/2000	IND 56,553	#032	Protocol Amendment: Change in Protocol 13C214; "Addition of Daniel Paulson, MD to Protocol . . ."
12/19/2000	IND 56,553	#033	Request for Special Protocol Assessment.
12/19/2000	IND 56,553	#034	Information Amendment: Clinical: Statistical Analysis; "The submission of statistical analysis plans for a pivotal trial and a final clinical study . . ."
12/21/2000	IND 56,553	#035	Information Amendment: Pharmacology/Toxicology: Final Study; "Submission of two drug disposition studies, one in the rat and one in the dog . . ."

Date	IND/NDA	Serial or Amendment #	Activity
12/21/2000	IND 56,553	#036	Information Amendment: Chemistry; including "Amending the subject IND to provide for the submission of data on a new manufacturer . . ."
01/04/2001	IND 56,553	#037	Annual Report, including updates on Phase 1 and 2 studies conducted during the year
01/04/2001	IND 56,553	#038	Press Release of Phase II trial results of studies with ADL 8-2698 in opioid bowel dysfunction.
01/19/2001	IND 56,553	#039	Request for End of Phase II Meeting with the Division for ADL 8-2698.
02/09/2001	IND 56,553	#041	End of Phase II CMC Pre-Meeting Package.
02/09/2001	IND 56,553	#042	End of Phase II Pre-Meeting Package (Briefing Document).
02/09/2001	IND 56,553	#043	Protocol Amendment: New Protocol, New Investigators, including "Submit new protocol under trial #14C302. Also submitted new investigators . . ."
03/02/2001	IND 56,553	#044	General Correspondence, including disk with revised list of attendees.
03/13/2001	IND 56,553		End of Phase II Meeting for ADL 8-2698.
03/22/2001	IND 56,553	#045	Minutes from the End of Phase II Meeting for ADL 8-2698.
04/11/2001	IND 56,553	#048	Protocol Amendment: New Protocol/New investigators; Amended IND to include a new Protocol 13C217.
06/14/2001	IND 56,553	#052	Protocol Amendment: Change in Protocol; Change in the statistical section of Protocol 13C217.
07/05/2001	IND 56,553	#059	Response to FDA Request for Information.
08/21/2001	IND 56,553	#065	Response to FDA Request for Information.
11/13/2001	IND 56,553	#073	Information Amendment: Chemistry, Manufacturing & Controls; Request for Comment
12/04/2001	IND 56,553	#031	General Correspondence: "Response to Division minutes from our October 16, 2000 meeting."
12/05/2001	IND 56,553	#077	Information Amendment: Clinical (Statistical Analysis Plans for Phase III Protocols.
01/15/2002	IND 56,553	#088	Annual Report, including updates on clinical studies conducting during the year
03/01/2002	IND 56,553		Adolor and FDA face to face meeting to continue discussions on development plan
04/09/2002	IND 56,553	#099	Minutes of Meeting with Division (March 1, 2002)

Date	IND/NDA	Serial or Amendment #	Activity
06/07/2002	IND 56,553	#104	IND Safety Report: Initial Written Report
09/05/2002	IND 56,553	#113	Protocol Amendment: Change in Protocol, Information Amendment: Clinical
10/03/2002	IND 56,553	#118	Information Amendment: Clinical; Submitted a Final Clinical Study Report 13C214 to the IND
12/16/2002	IND 56,553	#130	Information Amendment: Pharmacology Toxicology
01/06/2003	IND 56,553	#134	Annual Report, including updates on Phases 1, 2, and 3 studies conducting during the year
03/17/2003	IND 56,553	#143	IND Safety Report: Follow-up to a Written Report
08/01/2003	IND 56,553	#154	Information Amendment: CMC; Microbial issue
12/16/2003	IND 56,553	#172	Clinical: Statistical Analysis Plan Addendum
01/05/2004	IND 56,553	#177	Annual Report for 2003
02/13/2004	IND 56,553		FDA Letter granting Fast-Track Status Approval
02/23/2004	IND 56,553		Adolor and FDA face to face meeting to discuss NDA submission
02/25/2004	IND 56,553		Adolor and FDA face to face meeting to discuss CMC section of NDA submission
04/30/2004	IND 56,553		Telephone call from FDA granting Adolor request to file the NNDA under the Pilot 1, Continuous Marketing Application program.
05/04/2004	IND 56,553		NDA Pharm/Tox Submitted under CMA Pilot 1 Program as Reviewable Unit #1
05/27/2004	IND 56,553		NDA CMC Submitted under CMA Pilot 1 Program as Reviewable Unit #2
06/25/2004	NDA 21,775		Full NDA Submission
09/07/2004	NDA 21,775		Letter from FDA accepting NDA for review and defining PDUFA date as 4/25/05
09/24/2004	NDA 21,775		NDA Amendment #1 – change of address for Drug Product Packager
10/22/2004	NDA 21,775		NDA 120-Day Safety Report
01/10/2005	IND 56,553	#214	IND Annual Report
01/20/2005	NDA 21,775		Submission of Request for Meeting to discuss GSK Study 001
01/24/2005	NDA 21,775		FDA Request for Clinical Pharmacology Information
01/26/2005	NDA 21,775		Submission of Response to Request for Information: Clinical Pharmacology

Date	IND/NDA	Serial or Amendment #	Activity
01/28/2005	NDA 21,775		NDA Amendment #2 – Submission of GSK Study 001 Clinical Data
01/28/2005	NDA 21,775	Amendment #002	Submission of GSK #001 study data
02/14/2005	NDA 21,775		Submission of Briefing Document for 3/16/2005 meeting
03/3/2005	NDA 21,775		FDA Letter acknowledging Reviewable Unit 003 as an error and acknowledging the full NDA was received June 25, 2004.
03/14/2005	NDA 21,775		Receipt of FDA responses to Adolor's questions for 3/16/2005 meeting
03/16/2005	NDA 21,775		FDA/Adolor Face-to-Face Meeting
04/08/2005	NDA 21,775	Amendment #003	Submission to NDA of Final Clinical Study Report for GSK #001
04/18/2005	NDA 21,775		Receipt of FDA Meeting Minutes for 3/16/05 face-to-face meeting
04/19/2005	NDA 21,775		FDA letter postponing PDUFA date by 90 days due to Major Amendment #003
04/21/2005	NDA 21,775		Submission of Briefing Document for 5/24/2005 meeting to discuss statistical methodology (meeting did not occur)
05/19/2005	NDA 21,775		Response to Request for Information: Clinical Pharm (request received in email)
05/26/2005	NDA 21,775		Response to Request for Information: Clinical Pharm and Biopharm (request received in fax)
06/01/2005	NDA 21,775		Response to Request for Information: Biopharmaceutics Information (request received in email)
06/20/2005	IND 56,553	Serial #227	Submission: Protocol Amendment: Change in Protocol, New Investigator
07/14/2005	NDA 21,775		Submission of Response to Request for Revised Indication in the NDA labeling
07/21/2005	NDA 21,775		FDA Action Letter to NDA, "Approvable"
07/22/2005	NDA 21,775		Submission of Response to Action Letter and Request for Meeting to discuss content of Adolor's complete response letter
07/25/2005	NDA 21,775		Receipt of FDA Request for Clinical Pharmacology and Biopharmaceutical Data (Pop PK analyses).

Date	IND/NDA	Serial or Amendment #	Activity
08/05/2005	NDA 21,775		Receipt of FDA Confirmation of 9/7/2005 Face–to-Face Meeting
08/17/2005	NDA 21,775		Submission of Desk Copy to Project Manager of 7/22/2005 submission
08/22/2005	NDA 21,775		Submission of Briefing Document for 9/7/2005 Face-to-Face Meeting
09/07/2005	NDA 21,775		FDA/Adolor Face-to-Face Meeting for discussion of complete response to action letter
09/20/2005	IND 56,553	#230	Submission: Protocol Amendment: New Investigator
10/06/2005	NDA 21,775		FDA Letter received regarding endpoint discussion for Study 314
10/14/2005	NDA 21,775		Submission of Statistical Analysis Plan for Complete Response
10/24/2005	NDA 21,775		Receipt of FDA letter requesting Opioid consumption analyses
11/04/2005	NDA 21,775		Submission of Response to Request for Information (opioid consumption analysis)
11/20/2005	IND 56,553	#232	Submission: Protocol Amendment: New Investigator
12/15/2005	NDA 21,775		Receipt of FDA Letter of Comments to the Statistical Analysis Plan submission
12/19/2005	NDA 21,775		FDA/Adolor Telephone Conference re Complete Response
01/16/2006	NDA 21,775		Submission of Statistical Analysis Plan for Study 14CL314 and NDA Complete Response
01/31/2006	NDA 21,775	Amendment #004	Submission of CMC to cover 12 mg capsules and updated methodology
02/09/2006	IND 56,553	#241	Submission: Protocol Amendment: New Protocol, New Investigator
02/24/2006	NDA 21,775		Submission of FDA Requested Clinical Pharmacology and Biopharmaceutical Data (request from FDA 7/25/2005)
03/02/2006	IND 56,553	#244	Submission: Initial Safety Report - GSK SAE
03/22/2006	IND 56,553	#246	Submission: Information Amendment: CMC
04/10/2006	IND 56,553	#248	Submission: Safety Report: Follow-up GSK SAE
04/20/2006	IND 56,553	#250	Submission: Protocol Amendment: New Investigator
05/09/2006	NDA 21,775		Resubmission of NDA (submission of Complete Response to Action Letter)

Date	IND/NDA	Serial or Amendment #	Activity
06/07/2006	NDA 21,775		Submission of minor amendment to Complete Response (updated 2 tables)
06/15/2006	IND 56,553	#258	Submission: Protocol Amendment: New Investigator
07/12/2006	NDA 21,775		Letter to FDA Requesting 90 Day Review Meeting
07/27/2006	NDA 21,775		Fax from FDA - 90 Day Review Meeting Granted
08/17/2006	NDA 21,775		To FDA Briefing Document re 9/18/06 Meeting
08/18/2006	IND 56,553		Letter Received from FDA – Combined Annual Report Granted
08/23/2006	NDA 21,775		Letter Received from FDA – Information Request – Refer to June 25,2004 NDA
09/06/2006	NDA 21, 775		Letter Received From FDA – Information Request Letter
09/08/2006	NDA 21,775		Fax Letter from FDA – Information Request, Per BioPharm Reviewer
09/13/2006	NDA 21,775		Letter to FDA Response to Request for Information, Labeling
09/14/2006	NDA 21,775		Email from FDA – Meeting Response – 90 Day 2nd Cycle Meeting
09/15/2006	NDA 21,775		Response to Information Request – Clinical Pharmacology
09/21/2006	NDA 21,775		Response to Information Request of 9/18/06 Meeting
09/25/2006	NDA 21,775		Fax Request from FDA – Information Request Additional Clinical and Statistical Data
09/27/2006	NDA 21,775		Response to FDA re Information Request of September 25, 2006
10/03/2006	NDA 21,775		Fax Request from FDA – Information Request – Summary of CV Events in POI
10/04/2006	NDA 21,775		Letter and Listings to FDA in response to Information Request of 10/03/06– Summary of CV Events in POI
11/06/2006	NDA 21,775		Letter to FDA – Response to Action Letter and Meeting Request
11/08/2006	NDA 21,775		FDA Letter Received Noting Receipt of Submission and Approvable
11/09/2006	NDA 21,775		Letter to FDA Requesting Face-to-Face Meeting re Approvable Letter of 11/3/06
11/17/2006	NDA 21,775		Letter from FDA Granting Meeting Request –Refer to Letter of 11/09/06 to FDA

Date	IND/NDA	Serial or Amendment #	Activity
11/21/2006	NDA 21,775		To FDA – Briefing Document
11/29/2006	NDA 21,775		Fax from FDA re Preliminary Responses to Questions included in 11/21/2006 Background Info for Post Action Meeting
01/18/2007	NDA 21,775		Letter to FDA -Response to Request for Information – Clinical Pharmacology
05/11/2007	NDA 21,775		Letter to FDA – Capsules and Telephone Conference
06/06/2007	IND 56,553		Letter from FDA – Full Clinical Hold
06/15/2007	NDA 21,775		Letter to FDA – Proposed Content of Complete Response
08/09/2007	NDA 21,775		Letter to FDA – Complete Response to Approvable Letter
08/10/2007	NDA 21,775		Letter from FDA – Requesting Bone Marrow Study/2-yr Carc for Complete Response
08/27/2007	NDA 21,775		Letter from FDA – Receipt on 8/10/2007of Response from 8/09/2007
09/12/2007	IND 56,553		Letter from FDA – Clinical Hold
10/09/2007	NDA 21,775		Letter from FDA – Information Request – Clinical Data
12/17/2007	NDA 21,775		Submission to FDA: Briefing Document
12/28/2007	NDA 21,775		Letter to FDA – Response to Information Request of 12/20/2007
01/17/2008	NDA 21,775		Letter from FDA - RiskMAP Proposal
01/17/2008	NDA 21,775		Letter from Executive CAC
02/08/2008	NDA 21,775		Letter from FDA – RiskMAP proposal received
02/28/2008	NDA 21,775		Letter from FDA - Mouse, Rat Carc Comments
03/05/2008	NDA 21,775		Letter to FDA – Response to Information Request – Study Report 13CL130
03/06/2008	NDA 21,775		Letter to FDA – Cystecomy Synopsis
04/04/2008	NDA 21,775		Letter from FDA – Advice Letter – Proposed Labeling
04/14/2008	NDA 21,775		Submission of Revised Proposed Labeling
04/15/2008	NDA 21,775		Submission of Pediatric Plan
04/15/2008	NDA 21,775		Submission of Revised Proposed Labeling Based on FDA Feedback from 4/14/2008 Teleconference
04/17/2008	NDA 21,775		Submission of Revised RiskMAP

Date	IND/NDA	Serial or Amendment #	Activity
05/01/2008	NDA 21,775		Correspondence to FDA. L. Young to D. Griebel. Per E-mail from M. Scherer 25- April-2008. Response to Information Request – Revised Carton and Blister Packaging
05/02/2008	NDA 21,775		Correspondence to FDA Per E-mail fm M. Scherer 2-May-2008: Response to Information Request – Final Draft Labeling (PI)
05/02/2008	NDA 21,775		Correspondence to FDA Per E-mail fm M. Scherer 29-Apr-2008: Response to Information request – Final Draft RiskMAP
05/06/2008	NDA 21,775		Telephone Contact: M. Scherer to L. Young regarding Marketing Exclusivity Request on Labeling Changes - Still on schedule for PDUFA date
05/09/2008	IND 56,553		Correspondence from FDA. J. Korvick to L. Young. Clinical Hold lifted
05/14/2008	NDA 21,775		Correspondence from FDA. J. Beitz to L. Young. Information Request – REMS Requirements
05/15/2008	NDA 21,775		Correspondence to FDA: Response to Information Request – REMS Submission
05/20/2008	NDA 21,775		Correspondence from FDA. J. Beitz to L. Young. Approval Letter

EXHIBIT 15

AUTHORIZATION TO ACT ON BEHALF OF ASSIGNEE IN APPLICATION FOR PATENT TERM EXTENSION

Eli Lilly and Company, a corporation created and existing under the Laws of the State of Indiana, represents that it is the record owner of United States Patent No. 5,250,542, by reason of an assignment from the inventors thereof recorded on July 1, 1993 at Reel 006585, Frame 0364, hereby authorizes the below named registered practitioner to act on its behalf before the United States Patent and Trademark Office and the United States Food and Drug Administration with respect to the Application for Extension of Patent Term Pursuant to 35 U.S.C. § 156 seeking the extension of U.S. Patent No. 5,250,542.

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Eli Lilly and Company

By: Douglas K. Norman

Date: April 22, 2008

Douglas K. Norman
Print Name

Vice President and General Patent Counsel
Title